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THE THERMAL DECOMPOSITION OF ALLYLTRIMETHYLAMMONIUM HYDROXIDE

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Current studies in this Laboratory involve the thermal decomposition of certain allylic trimethylammonium hydroxides. The observation that quite appreciable amounts of dimethylamine and saturated carbonylic compounds are formed in these reactions has led to the belief that these quaternary bases rearrange to some extent during the pyrolysis, giving vinylic trimethylammonium bases. Although it is conceivable that the carbonylic products might be formed by the rearrangement of allylic alcohols derived from the unrearranged quaternary bases, the only readily understood mechanism by which dimethylamine could be formed involves the hydrolysis of a vinyldimethylamine, formed by an S_N2 attack by hydroxyl ion upon a methyl group of the vinyltrimethylammonium ion. The products of such a reaction would be methanol and a vinyldimethylamine, which would be hydrolyzed (in the dilute acid commonly used to absorb the bases formed in Hofmann degradations) to dimethylamine and a saturated carbonylic compound.[2] A thorough examination of the products formed in the thermal decomposition of the simplest allylic trimethylammonium hydroxide (I) was considered worth while to substantiate these findings and postulates.

The pyrolysis of I has not been studied for over half a century,[3] and then only cursorily. In an obscure publication which appeared in 1886 and has since been overlooked or discredited, Bono (3) heated allyltrimethylammonium iodide with potassium hydroxide and obtained an aldehyde, $C_6H_{10}O$, whose boiling point, 130–135° (as he pointed out) corresponded to that of α-methyl-β-ethylacrolein (IV), the only aldehyde of that formula known at that time; since our findings (see below) substantiate Bono's identification of this product,[4] the question mark appearing in Beilstein's account (5) of his work should be deleted. A short time

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[2] A similar hydrolysis has been proposed by Buchman, Schlatter, and Reims (1) to explain the formation of cyclobutanone and dimethylamine in the thermal decomposition of trans-1,2-cyclobutane-bis-(trimethylammonium)hydroxide; this decomposition presumably proceeds stepwise, over an intermediate vinylic (or allylic) trimethylammonium base.

[3] Quite recently, with reference to application of the decomposition of an allylic quaternary ammonium base to the synthesis of vitamin A, Milas (2) has written that "trimethylallylammonium hydroxide gives, on heating, chiefly trimethylamine and allyl alcohol" without any further substantiation of this statement.

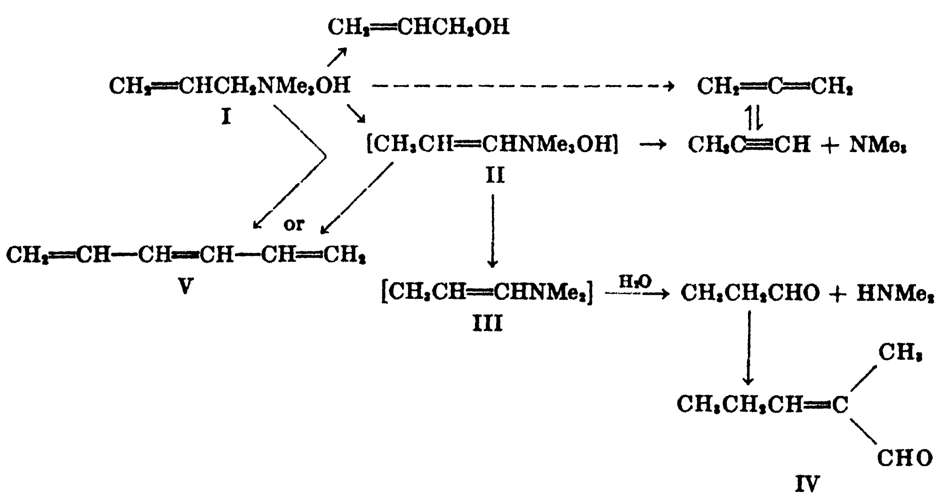
[4] It seems highly probable that the "ketone", $C_6H_{10}O$, b.p. 130–140°, semicarbazone m.p. 192°, reported by von Braun (4) as one of the pyrolysis products of propane-1,3-bis-(trimethylammonium)hydroxide, is in reality IV, formed *via* I. The formation of rather large amounts of allyldimethylamine in this reaction probably involves a different intermediate [(3-dimethylaminopropyl)trimethylammonium hydroxide] in view of our investigation of the bases formed in the pyrolysis of I.

later Collie and Schryver (6) studied the thermal decomposition of I with the object of preparing allyldimethylamine, traces of which were apparently identified; they claimed that another product of the reaction was acrolein, "recognized by its smell and the power it possessed of reducing a silver solution". Although other products of the pyrolysis of I may well have been responsible for these qualitative observations of Collie and Schryver, it is interesting that Hey and Ingold (7) have claimed the identification of acrolein (as its *p*-nitrophenylhydrazone) among the products of the decomposition of diallyldibenzylammonium hydroxide; in accord with our views of the changes effected by heating bases of this type, Hey and Ingold also reported the formation of dibenzylamine in this reaction; but the other hydrolysis product (propionaldehyde) of the supposed intermediate (β-methylvinyl)dibenzylamine was not detected by them.

Rothstein (8) has shown that the isomerization (I $\rightarrow$ II) of allyltrimethylammonium chloride in strongly basic media does not occur to any appreciable extent under conditions considerably milder than those employed in our experiments; he noticed that some dimethylamine was formed under less mild conditions, but failed to comment on this observation. We have attempted without success to identify the rearranged base (II) in a sample of partially pyrolyzed I; II evidently decomposes quite rapidly, once formed.[5]

To the best of our knowledge, the purely olefinic products of the thermal decomposition of I have not been investigated.

The substances we have identified among the products of this reaction (carried out at 310–325°) and the manner in which we believe they are formed are indicated in the following diagram:



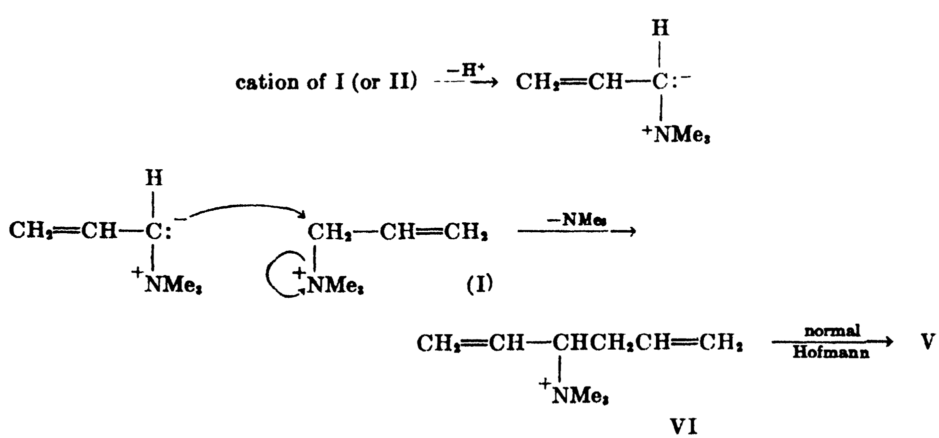
[5] In connection with this discussion of rearrangements occurring in the decomposition of allylic quaternary ammonium bases, recent work of Tarbell and Vaughan (9) with allylphenyldimethylammonium 2,6-dimethylphenoxide is of interest; N,N-dimethylaniline and the allyl ether of 2,6-dimethylphenol are formed in good yield. The predominant direction of this reaction to give this allyl ether (in analogy with the formation of allyl alcohol from I) is probably attributable to the different basic strength of the dimethylphenoxide ion.

Careful fractional recrystallization of the picrates prepared from the basic products of the decomposition showed that they consisted almost entirely of di- and tri-methylamines in a ratio of 1:2; we were unable to detect allyldimethylamine.

Among the neutral products boiling above room temperature, the following compounds were identified (by conversion to solid derivatives and comparison of these with authentic samples): propionaldehyde (trace), allyl alcohol (2.4%), and α-methyl-β-ethylacrolein (IV) (9.2%); higher-boiling materials, probably consisting of propionaldol and other aldehyde and polyene condensation products, were isolated but not identified. From the most volatile portion of this neutral fraction, a water-insoluble oil was isolated and shown (by its ultraviolet absorption spectrum, Figure 1, upper curve) to contain about 2% (yield at least 0.06% from I) of 1,3,5-hexatriene (V);[6] the presence in this oil of a conjugated diene was also indicated by the absorption spectrum [compare products reportedly formed by the dimerization of allene (12)].

Distillation of the more volatile neutral products gave a 34% yield of a mixture of methylacetylene and, presumably, allene; the identification of the former as the major constituent was indicated by the boiling point (principally at −23°) and confirmed by the preparation of mercuric methylacetylide from it in good yield. Analysis of a small sample of gas withdrawn from this mixture provided data from which it was possible to estimate its composition as 87.2% methylacetylene and 12.8% allene. According to Slobodin (13), an equilibrium mixture of 61.5% methylacetylene and 38.5% allene is rapidly formed on passing

[6] The detection of this product recalls an example of the so-called "1,1-elimination" described by Ingold and Jessup (10); analogy with this work would represent the formation of V by the dimerization of $CH_2{=}CH\ddot{C}H$ (which could be formed from I or II by abstraction of a proton and loss of trimethylamine), but it is difficult to see how such a reactive intermediate would have sufficient opportunity to dimerize to give detectable amounts of V. The following mechanism seems more reasonable:



VI

Note that Kharasch and co-workers (11) have shown that intermediates analogous to VI are involved in the formation of 1,3,5-hexatrienes from allyl chlorides by the action of sodamide.

either of the pure gases over "floridin" at 325°. It is thus clear that the methylacetylene formed in the pyrolysis of I at 310–325° is not an isomerization product of allene; in fact, although some of the allene may arise directly from I (see broken arrow in diagram), all of it may well be formed from methylacetylene.

In agreement with the postulated step II → III, the pyrolysis of neurine (vinyltrimethylammonium hydroxide) is reported (14) to yield some vinyldimethylamine; acetaldehyde and trimethylamine were also formed, but whether or not any acetylene was produced is not indicated.

The author wishes to acknowledge his indebtedness to Dr. E. R. Buchman for helpful discussions during the course of the investigation; and to The Research Corporation for the support of this research.

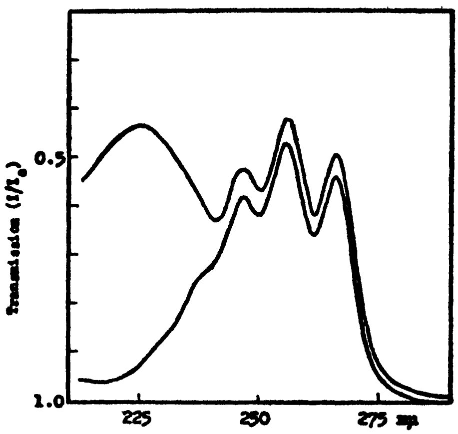


FIGURE 1. Upper curve: 1.8 mg. hydrocarbon (b.p 52–72°) in 25 ml. *n*-hexane. Lower curve: 2.9 mg. authentic 1, 3, 5-hexatriene in 2.5 l. *n*-hexane

EXPERIMENTAL PART

All melting points are corrected. Microanalyses were done at this Institute by Dr. G. Oppenheimer and her staff. Absorption spectra were obtained using a Beckman Model DU Spectrophotometer.

The pyrolyses were carried out in an apparatus similar to that used previously in this Laboratory (15). The decomposition chamber was prepared by blowing a test-tube bottom on the female half of a 24/40 standard taper joint to give a tube 11 cm. in depth; the male half was similarly closed off 2 cm. above the grinding and a 50-ml. Squibb funnel sealed into it in such a way that the tip of the funnel extended almost to the ground part of the joint; a 16-cm. straight condenser set for downward distillation was also sealed to this (male) half of the joint, near the point-of-entrance of the funnel stem. Both halves were fitted with hooks so that they might be held together snugly (with small springs) during the decomposition. The condenser (cooled by circulating ice-water) led to a wash-bottle (in the larger experiment described below an empty vessel preceded this) containing an appropriate amount of 6 *N* hydrochloric acid and cooled in ice; any products passing this bottle were conducted through a small amount of calcium chloride and into a series of two traps cooled in Dry-Ice-dibutyl ether (no appreciable amount of material collected in the second of these, whose exit was protected from moisture by a calcium-chloride tube). Before running a pyrolysis, the apparatus was swept out with nitrogen and the decomposition chamber charged with about 4 g. of 20–40 mesh powdered Pyrex glass and heated (in a

metal-bath extending about 5 cm. up the chamber) to 310–325°. A concentrated aqueous solution of I was then introduced dropwise from the funnel under a water-head of about 45 cm.

First experiment. A concentrated aqueous solution of 11.4 g. (0.0633 mole) of dry allyltrimethylammonium bromide (16) was shaken for 15 minutes with silver oxide prepared from 17.0 g. (0.1 mole) of C.P. silver nitrate and carbonate-free aqueous sodium hydroxide (17). Solids were filtered from the solution and the filtrate freed of most of its water *in vacuo* (water-aspirator) at 40–50°. The residual syrup was pyrolyzed (as indicated above) over a period of about two hours; the acid-wash bottle (initially charged with 15 ml. of acid) now contained a floating layer of yellow oil, and about 1 ml. of colorless mobile liquid had collected in the Dry-Ice trap.

The aqueous phase of the distillate was saturated with sodium sulfate, washed with three 10-ml. portions of ethyl ether, and divided into three equal parts. The bases in one of these portions were converted to picrates by treating with 5.0 g. (theory 1.2 g.) of sodium hydroxide pellets in an evacuated manifold in communication with a flask containing 500 ml. (slight excess) of a 1% solution of picric acid in ethyl ether; after the manifold had stood overnight at room temperature, the crude picrates, filtered off, washed with ether, and air-dried, weighed 4.7 g. Recrystallization of this material from methanol, followed by mechanical separation of the bright yellow needles (trimethylamine picrate, m.p. 224–225°) from the rugged dark, red-brown prisms (dimethylamine picrate, m.p. 158–161°) gave 3.12 g. (51.3%) of the former and 1.49 g. (25.7%) of the latter——total recovery 4.61 g.[7]

Another third of this solution of the bases formed in the pyrolysis was cooled and treated with 1.2 ml. (0.01 mole) of benzoyl chloride and 10 ml (0.05 mole) of 5 *N* sodium hydroxide; after warming to room temperature, the strongly basic mixture (which no longer smelled of benzoyl chloride) was extracted with benzene. Drying and evaporating this benzene extract gave 0.81 g. (25.8%) of N,N-dimethylbenzamide, crude m.p 43–44°, not raised by recrystallization from ethyl acetate. The benzene distilled from this derivative of dimethylamine was extracted with 10 ml. of 6 *N* hydrochloric acid and this extract placed in the receiver of a distilling apparatus in the boiler of which the basic aqueous solution (from which the dimethylbenzamide was extracted with benzene, above) was heated until its vapors were no longer basic. Evaporation of the distillate to dryness left 1.11 g. of white hygroscopic crystalline material; a negligible part of the bases (in which any dimethylallylamine should presumably be concentrated) liberated from this salt boiled above room temperature.

The material (*ca.* 1 ml., see above) collected in the Dry-Ice trap was allowed to warm to room temperature and thus (except for about 0.1 ml. of higher-boiling material) distilled through a short tube of Drierite into an ampule cooled in Dry-Ice, yield 0.67 g. (34%)[7] of a mixture of methylacetylene and allene (see below); the action of Nessler's reagent on this material, following the directions of Johnson and McEwen (18), gave 1.03 g. (44%) of crude mercuric methylacetylide; continuous extraction with acetone gave white flaky crystals, m.p. 209° dec. [lit. (18), m.p. 203–204° (uncorr.)].

Second Experiment. A concentrated aqueous solution of allyltrimethylammonium bromide was prepared as follows: in a flask kept cold by immersion in an ice-bath, 65 g. (0.50 mole) of allyl bromide (Eastman White Label) was carefully layered with 120 g. (theory 115.6 g.) of a 25.5% solution of trimethylamine in water; as the two layers slowly merged, the mixture was cautiously swirled from time to time; solution of the last of the allyl bromide was accomplished by shaking the mixture at room temperature for a short time. Excess trimethylamine was then expelled by bringing the solution to its boiling point. After cooling, it was shaken for 15 minutes with silver oxide from 100 g. (theory 85 g.) of silver

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[7] From the fact that only 77% of the theoretical quantity of bases is obtained, it must be concluded that about 23% of the starting quaternary ammonium base is lost during the concentration *in vacuo* at 40–50°; this conclusion is taken into consideration in calculating the yields of products.

nitrate. The resulting aqueous solution of I was concentrated (seven hours) and pyrolyzed (two hours) as before.

Redistillation of the liquid collected in the Dry-Ice trap gave 5.59 g. (34%)[7] of material boiling principally at −22.7° (pentane thermometer immersed in boiling liquid) at 746 mm., in agreement with a recent value given (19) for the boiling point of methylacetylene. A 43.5-ml. sample of gas removed from this liquid was analyzed in a modified Bunte apparatus (20), absorbing the methylacetylene in Nessler's reagent and the allene in 82.5% sulfuric acid (21); from the values thus obtained (16.6% allene in methylacetylene) and the vapor-pressure-temperature equations given by Livingstone and Heisig (22) for these two substances, it can be calculated that the liquid from which this small sample of gas was removed contained 12.8% allene.

Somewhat less than 1 ml. of the original methylacetylene-allene fraction was not volatile at room temperature; this brownish oil was added to the two-phase distillate collected just before the acid-wash bottle (see above); with cooling, the contents of the latter were also added. The oily epiphase, which decreased somewhat in volume during this acidification, was taken up in ether (after saturating the aqueous phase with sodium sulfate), dried over sodium sulfate and magnesium sulfate, and the ether carefully fractionated off at atmospheric pressure. The residual oil (somewhat less than 10 ml.) was transferred to a smaller flask and divided into the following fractions by distillation through a 10-cm. Vigreux column: A, 1.28 g., b.p. 25–27° at 100 mm. B, 1.38 g., b.p. up to 60° at 100 mm. C, 1.87 g., b.p. 53–50° at 50 mm. D, 1.15 g., b.p. up to 70° at 0.6 mm. The residue weighed 1.95 g. (Total yield of neutral materials, about 70%).[7]

Preliminary qualitative tests on A showed that it contained some carbonylic constituent and was only partly water-soluble; it was shaken with 2.0 g. of saturated aqueous sodium bisulfite and the insoluble oil carefully pipetted off, dried over magnesium sulfate, and distilled at atmospheric pressure, giving 0.51 g. of colorless, brilliant oil, b.p. 52–72°, having a characteristic olefinic odor. The ultraviolet absorption spectrum of a solution of 1.8 mg. of this material in 25 ml. of pure *n*-hexane showed four peaks, λ_{max} 225, 247, 256, and 266 mμ; the shape and location of the three peaks at longer wavelengths were indistinguishable from those observed (see Fig. 1) on a solution of authentic 1,3,5-hexatriene (see below). The intensity of absorption at 256 mμ (I/I_0 = 0.422) compared with that of the same peak of pure authentic hexatriene indicated the presence of 1.86% of this triene in the above water-insoluble fraction, representing a yield of 0.064%[7] from I; this must be regarded as a minimum yield because of the sensitive nature of this triene and the fact that it was an unexpected product and no special precautions were exercised during its concentration. The 225-mμ peak is quite alien to the spectrum of 1,3,5-hexatriene and may indicate the presence of some conjugated diene in this fraction; such a diene may also be the source of a crystalline product (rugged colorless granules left on spontaneous evaporation of a ligroin-benzene solution, m.p. 141–144°) obtained (in amount too small for analysis) by refluxing 0.20 g. of this fraction with a benzene solution of 0.24 g. of maleic anhydride [the maleic-anhydride-addition product of 1,3,5-hexatriene melts at about 50° (23)].

Treatment of the above bisulfite extract of fraction A with 7.0 g. of saturated aqueous sodium carbonate gave an ether extract having a distinct odor of propionaldehyde; the extract was treated dropwise with a 2,4-dinitrophenylhydrazine sulfate solution (24a) until a precipitate no longer formed in the drops descending through the ether solution. On shaking, this precipitate dissolved in the ether-phase, which was evaporated to dryness; the residue was twice recrystallized from acetonitrile, clusters of orange needles, m.p. 154.7–155.7°, undepressed by admixture with an authentic sample of propionaldehyde (25) 2,4-dinitrophenylhydrazone.

Fraction B, which gave a strong alcohol-test with ceric-nitrate reagent (24b), was redistilled at atmospheric pressure, giving 0.58 g. (2.4%)[7] of fairly pure allyl alcohol, b.p. 91–97.5°. Treatment of 0.12 g. of this material with pyridine and 3,5-dinitrobenzoyl chloride (0.5 equivalent) according to Suter (26) gave 0.20 g. of crude allyl 3,5-dinitrobenzoate, m.p. 45–48.5° (a like sample of authentic allyl alcohol, similarly treated, also

gave 0.20 g. of crude ester, m.p. 48–49°); this derivative was converted to the α-napththylamine complex (26), dark red needles from ligroin-benzene, m.p. 121–122°, unaffected by admixture with an authentic sample.

Fraction C was identified as α-methyl-β-ethylacrolein (IV) (9.2%)[7] by conversion of a sample to the 2,4-dinitrophenylhydrazone, bright orange-red clustered plates from acetic acid-acetonitrile, m.p. 161–162°; this material did not depress the melting point of the dinitrophenylhydrazone prepared from authentic IV [b.p. 54–56° at 47.5 mm.; prepared in 41% yield according to Grignard and Abelmann (27)]. The semicarbazone of this aldehyde has been reported to melt anywhere from 187–188° (28) to 207° (29) [see reference in footnote 4 to a compound, m.p. 192°, described by von Braun (4), which may be IV-semicarbazone]. As prepared by us, this derivative is apparently homogeneous (cis-trans isomerism of IV and syn-anti isomerism of its semicarbazone lead to the prediction of four possible forms), sparsely-clustered rough colorless bars from ethanol-water (Anal. Calc'd for $C_7H_{13}N_3O$: C, 54.17; H, 8.44; N, 27.08. Found: C, 54.49; H, 8.24; N, 27.48.), but the melting point varies considerably with the manner in which this constant is secured; heated very slowly from 180°, it melts at 192.2–192.5°; from 190°, at 202.9–203.4°; when inserted into baths maintained at constant temperatures, a clear melt was obtained in 24 seconds at 209° and in 16 seconds at 210°. The semicarbazone is thus not of very great value for the characterization of methylethylacrolein; literature values (30) for the melting point of the dinitrophenylhydrazone are all in substantial agreement.

Authentic 1,3,5-hexatriene (V) was prepared by the action of sodamide on a solution of allyl chloride in liquid ammonia, according to Kharasch and Sternfeld (23). The delicate nature of this triene is not sufficiently stressed by these authors in their directions for its preparation. In order to isolate appreciable quantities of the desired product, it is advisable to sweep vessels with nitrogen, used freshly-distilled ether, carry out distillations at reduced pressure, and add traces of hydroquinone to solutions of the triene which are to be allowed to stand for any length of time or are to be heated. A solution of the crude reaction product in ether was freed of ether and hexatriene by slowly reducing the pressure to 80 mm. and then heating the boiler slowly up to 100°; the distillate (b.p. up to 28°) was condensed in an efficient condenser cooled by circulating ice-water, and collected in a flask cooled in Dry-Ice. Toward the end of the distillation, the product crystallized on the tip of the condenser; this crystalline material (0.47 g.) was carefully removed and used as quickly as possible for the determination of the following physical constants: melting-range −35 to −28° (sample in a sealed capillary tube),[8] Emich micro-b.p. 74.5° at 748 mm., d_4^{24} 0.7385, n_D^{24} 1.4770; the lack of agreement among previously reported physical constants for 1,3,5-hexatriene (32) undoubtedly reflects the delicate nature of this substance. Kharasch and Sternfeld (23) report the b.p. of V as 76–80°; their values for n_D^{20} (1.4330) and for d_4^{20} (0.7182) both seem low. The crystallization of 1,3,5-hexatriene apparently has not been observed until now.[8] A solution of V in *n*-hexane gave an ultraviolet absorption spectrum (see Fig. 1) having the following characteristics: λ_{max} 247 mμ ($\epsilon \times 10^{-4}$, 1.63); 256 (2.24); 266 (1.85); data on this spectrum presented by its previous investigators (33) are insufficiently detailed for comparison. These three peaks, with the same relative intensities, but with hypso- or batho-chromic shifts of the group as a whole, are seen in the spectra of other compounds (34) having this system of three conjugated double bonds.[9]

[8] While this manuscript was being prepared, we received an abstract (31) of a paper by Woods and Schwartzman in which the following constants are reported for a sample of 1,3,5-hexatriene prepared in a different way: m.p. −11°, b.p. 79–80°; the ultraviolet spectrum is also reported, but details of the curve are not included in the abstract.

[9] Blout and Fields (35) do not present details of the spectrum of 2,4,6-octatriene, stating only that its peak of maximum intensity (at 263 mμ) has some fine structure. It is of interest that the ultraviolet absorption spectrum of 1,3,5-cyclooctatriene (36), in which the ring structure forces the three double bonds to maintain an "all-cis" configuration, is devoid of fine structure.

The remainder of the mixture of ether and V (*i.e.*, after removing the crystalline material as noted above) was treated with a few crystals of hydroquinone and distilled through a 20-cm. Vigreux column at 748 mm., giving, besides ether, a 0.7-ml. fraction, b.p. 68.3–74.7°, m.p. *ca.* −45° (thermometer in melt), and a 1.0 ml. fraction, b.p. 74.7–75.0°, m.p. *ca.* −35°.

SUMMARY

The thermal decomposition of allyltrimethylammonium hydroxide has been investigated.

Evidence is presented indicating that the pyrolysis of allylic quaternary ammonium hydroxides is accompanied by some isomerization to the corresponding vinylic quaternary ammonium bases.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE WASHINGTON SQUARE COLLEGE OF NEW YORK UNIVERSITY]

SYNTHETIC ESTROGENS. CYCLOHEXYL DIENESTROL AND HEXESTROL[1]

J. B. NIEDERL AND R. M. SILVERSTEIN

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Studies carried out in this laboratory have been concerned with the effects of ring substituents on synthetic estrogens of the dienestrol and hexestrol types. Thus far, aryl and aralkyl (1), tetra-alkyl (2), and di-alkyl (3) groups have been used.

In continuation of these studies, the cyclohexyl substituted dienestrol and hexestrol have been prepared along with some of their organic esters. The starting material was *o*-cyclohexylphenol; the general plan of synthesis is shown in the flow sheet.

EXPERIMENTAL

o-Cyclohexylphenylpropionate (*I*) (yield quantitative; b.p. 177° at 15 mm.), *3-cyclohexyl-4-hydroxypropiophenone* (*II*) (yield 75%; m.p. 150–152°), and *3-cyclohexyl-4-acetoxypropiophenone* (*III*) (yield 95%; b.p. 190–192° at 3 mm.) were prepared essentially by the same methods as the analogous compounds previously reported (1).

3,4-Bis-(m-cyclohexyl-p-acetoxyphenyl)-3,4-hexanediol (*IV*). A modification (3) of the classical pinacol reduction was utilized, involving ethyl acetate rather than ether as the solvent. Fifty grams of aluminum foil was cut into strips, crumpled loosely, etched with alkali, washed, amalgamated with 0.5% mercuric chloride, washed rapidly with water, ethanol and ethyl acetate, then covered with 500 ml. of ethyl acetate which had previously been saturated with water. One-third of a mole of (III) was added in one batch. The mixture was stirred for two hours during which time the temperature rose to 65° and dropped back to 35°. The aluminum hydroxide formed and the unreacted aluminum were filtered off and washed with ethyl acetate, which was then combined with the filtrate. About half of the ethyl acetate was removed by distillation, and the rest was allowed to evaporate from a wide, flat crystallizing dish over a period of several days. The result was a hard white solid mass covered by a viscous gum. The gum was removed by washing with petroleum ether. The solid, on recrystallization from dilute ethanol melted at 183–185°. The yield was 39%.

3,4-Bis-(m-cyclohexyl-p-acetoxyphenyl)-2,4-hexadiene (*V*). Seventeen grams of (IV) was refluxed for twenty minutes with 50 ml. of acetic anhydride and 30 ml. of acetyl chloride. The solution was cooled, poured into a large volume of ice-water, shaken vigorously, and allowed to stand for several hours with occasional shaking. The semisolid mass which separated was shaken with several changes of water, then triturated with a small amount of cold methanol until solidification was effected. The flaky solid was filtered, washed with methanol, and recrystallized from the same solvent. The yield after recrystallization was 80%. The product gave a positive unsaturation test with bromine, and melted at 175–177°. An additional amount of hexadiene was obtained from the petroleum ether solution of the pinacol gum by removing the solvent and treating the gum by the above procedure.

3,4-Bis-(m-cyclohexyl-p-hydroxyphenyl)-2,4-hexadiene (*VI*). Two grams of (V) was saponified by heating to 50° for two hours with Claisen solution and allowing to stand overnight at room temperature. On diluting with water, the sodium salt precipitated. Carbon

[1] This material has been abstracted from the Ph.D. Thesis presented by R. M. Silverstein to the faculty of the Graduate School of New York University.

dioxide was passed into this suspension until it was acid. The precipitate was filtered, washed, and recrystallized from dilute ethanol. The yield after recrystallization was 85%; m.p. 177–178°. Analysis indicated that this product was a monohydrate. On drying in a vacuum desiccator at 80° and 40 mm. for 8 hours, a correct analysis for the anhydrous substance was obtained.

3,4-Bis-(m-cyclohexyl-p-acetoxyphenyl)hexane (VII). Four grams of (V) was dissolved in 100 ml. of dioxane. One-tenth gram of palladium on carbon was added, and the mixture was shaken with hydrogen at 3 atmospheres and room temperature for one hour. The catalyst was filtered off, and the filtrate concentrated to about half its original volume. On slow evaporation of the remaining solvent, crystals were deposited. After washing with methanol, these crystals melted at 138–146°. A constant and sharp m.p. of 146–147.5° was obtained after three recrystallizations from dilute acetic acid. The final yield was 50%. A mixture of acetone and ethyl acetate (the hexadiene was insoluble in acetone alone) was

TABLE OF COMPOUNDS

	FORMULA	M.P., °C.	CALC'D C	CALC'D H	FOUND C	FOUND H
3-Cyclohexyl-4-hydroxypropionphenone	$C_{15}H_{20}O_2$	151–152	77.54	8.68	77.55	8.64
3-Cyclohexyl-4-acetoxypropiophenone	$C_{17}H_{22}O_3$	[a]	74.42	8.08	74.40	8.19
3,4-Bis-(*m*-cyclohexyl-*p*-acetoxyphenyl -3,4-hexanediol	$C_{34}H_{46}O_6$	183–185	74.14	8.42	74.14	8.51
3,4-Bis-(*m*-cyclohexyl-*p*-hydroxyphenyl)-2,4-hexadiene						
Free phenol monohydrate	$C_{30}H_{40}O_3$	177–178	80.31	8.99	80.48	9.09
Free phenol	$C_{30}H_{38}O_2$	177–178	83.67	8.89	83.55	8.83
Diacetate	$C_{34}H_{42}O_4$	175–177	79.34	8.22	79.48	8.43
Dipropionate	$C_{36}H_{46}O_4$	150–150.5	79.66	8.54	79.50	8.72
Dibenzoate	$C_{44}H_{46}O_4$	189–190.5	82.72	7.26	82.55	7.48
3,4-Bis-(*m*-cyclohexyl-*p*-hydroxyphenyl)-hexane						
Free phenol monohydrate	$C_{30}H_{44}O_3$	195–197	79.58	9.87	79.61	10.04
Free phenol	$C_{30}H_{42}O_2$	195–197	82.89	9.70	83.13	10.04
Diacetate	$C_{34}H_{46}O_4$	146–147.5	78.72	8.94	78.77	8.88
Dipropionate	$C_{36}H_{50}O_4$	138–139	79.08	9.22	79.02	9.25
Dibenzoate	$C_{44}H_{50}O_4$	195–197	82.20	7.84	82.17	7.63

[a] Boiling point 190–192° at 3 mm.

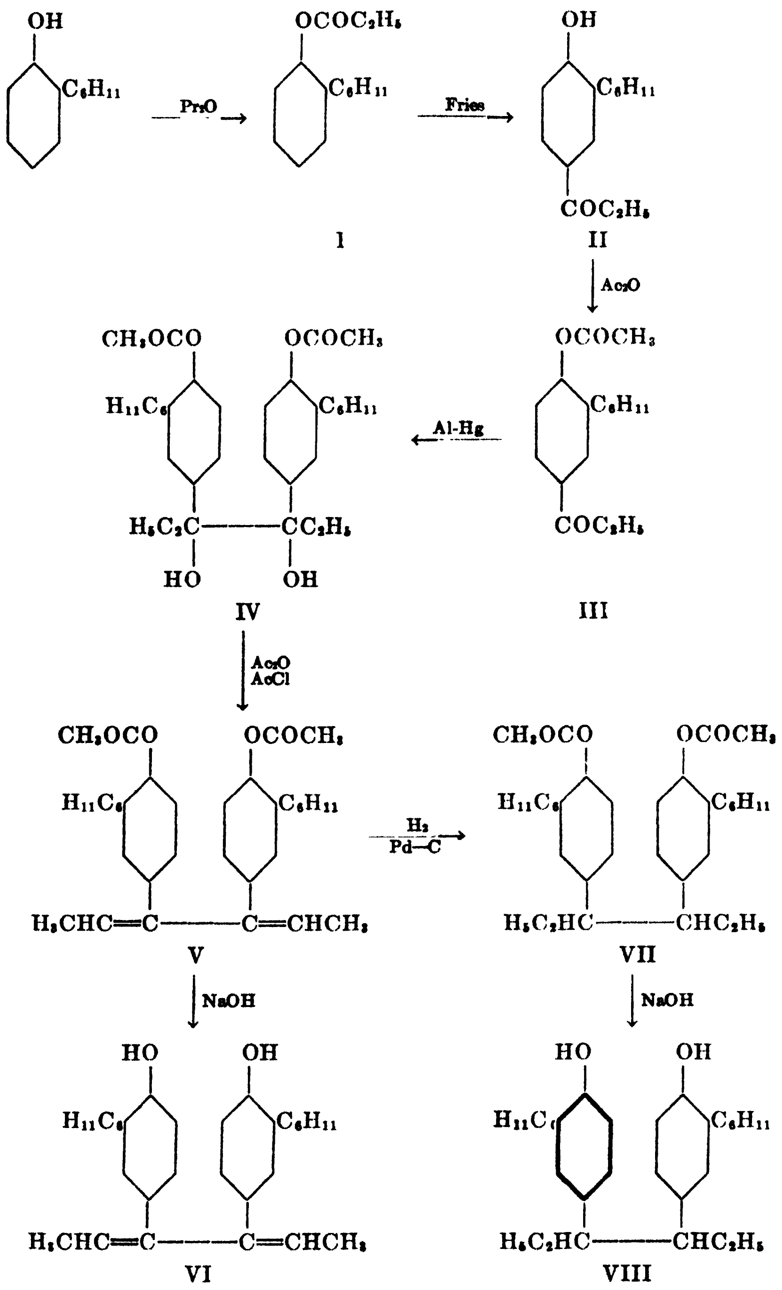
tried as the hydrogenation solvent, but was not as satisfactory as dioxane. The m.p. of this product before recrystallization was 120–144°.

3,4-Bis-(m-cyclohexyl-p-hydroxyphenyl)hexane (VIII). Two grams of (VII) was saponified with Claisen solution as under (VI), and recrystallized from dilute acetic acid. The yield after recrystallization was 85%; m.p. 195–197°. Analysis indicated that the product was a monohydrate. On drying in a vacuum desiccator at 80° and 25 mm. for 8 hours, a correct analysis for the anhydrous substance was obtained.

Esters. The dipropionates of (VI) and (VIII) were prepared by refluxing with propionic anhydride and recrystallizing from dilute acetic acid. The dibenzoates of (VI) and (VIII) were prepared by the Schotten-Baumann method, and recrystallized from an absolute ethanol-ethyl acetate mixture.

Pharmacology. Assays were performed according to standard procedure by subcutaneous injection into ovariectomized rats of oil solutions of the compounds. At the 50 gamma dose level, 3,4-bis-(*m*-cyclohexyl-*p*-hydroxyphenyl)hexane elicited estrogenic response in 10% of the animals tested.

FLOW SHEET



Acknowledgment. The authors wish to express their appreciation to the pharmacological laboratories of Reed and Carnrick, Jersey City, N. J., and of Lederle Laboratories, Pearl River, N. Y. for the estrogenic assays.

SUMMARY

In continuation of the work done in this laboratory in the field of synthetic estrogens, cyclohexyl substituted dienestrol and hexestrol have been prepared. The introduction of the cyclohexyl groups resulted in considerable diminution of estrogenic activity.

NEW YORK, N. Y.

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[CONTRIBUTION FROM KOPPERS CO., INC., MULTIPLE FELLOWSHIP ON TAR SYNTHETICS, MELLON INSTITUTE]

OXIDATION OF CERTAIN METHYLPYRIDINES TO PYRIDINE CARBOXYLIC ACIDS

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Since several relatively pure methylpyridines are now commercially available from coal tar, and since there are many contradictions and few quantitative data in the older literature on the oxidation of the methylpyridines, it was considered worth while to establish satisfactory preparative conditions for certain pyridine carboxylic acids. Much of the early work was qualitative in nature and dealt mainly with the proof of structure of the pyridine carboxylic acids and of their parent methylpyridines.

EXPERIMENTAL

All melting and boiling points are corrected.

Methylpyridines. The methylpyridines (Table I), with the exception of 2-methyl-5-ethylpyridine, were products of Koppers Co., Inc., with minimal purity of 95%. The yield figures of the pyridine carboxylic acids obtained therefrom are conservative, because 100% purities were assumed for the methylpyridines in the yield calculations. The purity of 2-picoline was determined by analytical distillation; the purities of 3- and 4-picolines and of 2,6-lutidine were established by the cryoscopic method described by Freiser and Glowacki (1). 2-Methyl-5-ethylpyridine was synthesized by the reaction of paraldehyde with aqueous ammonia (2); the purity of the product was not established.

Apparatus. The oxidation apparatus was a 5-liter, 4-necked flask, with one of the necks elongated six inches and water-cooled to allow portion-wise addition of permanganate without loss of alkylpyridine by volatilization. The other three necks were equipped with thermometer, mercury-sealed stirrer, and large-capacity reflux condenser, respectively. The dehydration-extraction apparatus was a 5-liter flask provided with stirrer and water trap (Fig. 1) surmounted by an efficient reflux condenser.

Titration, isoelectric points, and isolation of pyridine carboxylic acids. Both colorimetric and electrometric (glass electrode) titrations were satisfactory. The isoelectric points of picolinic, nicotinic, isonicotinic, and 6-methylpicolinic acids were found to be 3.2, 3.4, 3.6, and 3.3, respectively. It was shown that the precipitation *p*H could be varied 0.3 on either side of the isoelectric point without affecting the yield of acid. Dipicolinic acid (2,6-dicarboxypyridine), a relatively strong acid, was precipitated from 1.5 *N* hydrochloric acid; isocinchomeronic acid (2,5-dicarboxypyridine) was isolated as the dimethyl ester and subsequently hydrolyzed to the free acid.

Recoverable non-oxidized base. Although non-oxidized base was not recycled in the laboratory runs, the amount of recoverable base was determined in order to calculate oxidation efficiency. Recovery was accomplished by distilling the alkaline oxidation filtrate until the distillate was base-free. About 8% of the base was recoverable in the oxidation of the picolines to mono-acids and of 2,6-lutidine and 2-methyl-5-ethylpyridine to di-acids; 20% of the base escaped oxidation in the preparation of 6-methylpicolinic acid from 2,6-lutidine.

Identification of non-oxidized base. Recovered base from the oxidation of the picolines was analyzed in order to check on degradation to pyridine or accumulation of impurity. The recovered base in the distillate was salted out by potassium hydroxide, separated, dried by potassium hydroxide, further dried by azeotroping its benzene solution and finally distilled. In all cases the recovered base (identified as picrate) was the same as the starting material.

Non-decarboxylation during preparation. Picolinic, nicotinic, isonicotinic, and dipicolinic acids were unchanged by boiling for six hours in alkaline solutions similar to that of the oxidation filtrate; also in water solution, and in 1.5 *N* and 5 *N* aqueous hydrochloric acids. Therefore, it is unnecessary to protect their boiling aqueous solutions by inert gas, as practised by Meyer and Tropsch (3), or to lower the boiling temperature by the use of reduced pressure. Three grams of isonicotinic acid (99.8% pure) was heated for 9 days

TABLE I

CONSTANTS OF METHYLPYRIDINES

COMPOUND	B.P. (°C.)	PRESSURE (MM.)	n_D^{20}	d_4^{20}	FR.P. (°C.)	PURITY %
2-Picoline	128.7–128.9	747	1.5002	0.946	−66.6	98
3-Picoline	143.1–143.3	745	1.5060	0.956	−19.8	96
4-Picoline	144.2–144.4	743	1.5050	0.953	1.5	96
2,6-Lutidine	142.8–143.0	743	1.4977	0.925	−8.1	96
2-Methyl-5-ethylpyridine	177.4–177.6	738	1.4970	0.918	—	—

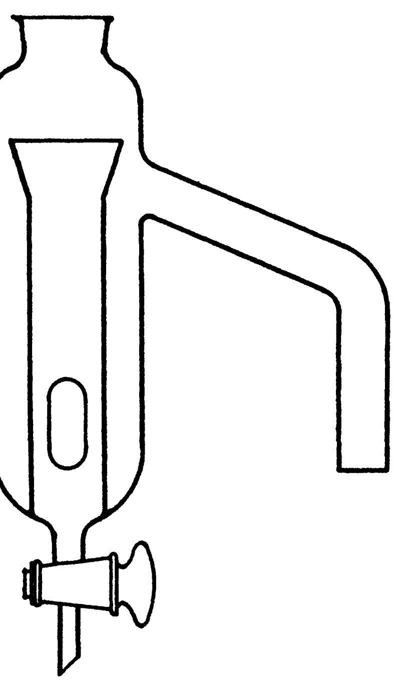

FIG. 1. WATER TRAP

at 110°; the weight loss was 0.1% per day, and the purity of the residual acid at the end of 9 days was 99.7%.

Picolinic acid (*4–19*) is very soluble in water (9 g. in 10 cc. of water at 9°). The present preparative method involves dehydrating the oxidation filtrate at its isoelectric point by azeotropic distillation with benzene and simultaneously extracting the picolinic acid. The solubility of picolinic acid in 1000 cc. of benzene at 15, 30, and 80° is 2, 4, and 41 g., respectively. Picolinic acid in boiling benzene (1% solution, boiled 20 hours) did not decompose. A similar experiment with a boiling xylene solution showed 36% decomposition of the acid.

(*A*) *Preparation.* Two hundred grams (2.15 moles) of 2-picoline and 2500 cc. of water were placed in the oxidation flask and 900 g. (5.7 moles) of crystalline potassium permanganate was added in ten portions during six hours. The first five additions were made at 70°, the last five at 85–90°. Each successive addition of permanganate, which was made only after the preceding amount had been consumed, was washed down the elongated neck with water (about 500 cc. total). After the last charge of permanganate had been decolorized, the hot reaction mixture was filtered by suction, and the manganese dioxide was washed on the filter with 1500 cc. of hot water in four portions, allowing each portion to soak into the cake without application of vacuum, finally sucking the cake dry before adding fresh wash water.

The combined filtrate-wash was concentrated to 700 cc. and the concentrate was set at *p*H 3.2 by adding about 265 cc. of concentrated hydrochloric acid. The solution was poured into the extraction flask and 3000 cc. of benzene was added. The flask was immersed in a water-bath at 90°, the reflux condenser was replaced by the water trap-condenser assembly, and the contents of the flask were stirred and boiled for about twelve hours until no more water collected in the trap. This dehydration-extraction produced a friable solid amenable to solvent extraction and was preferable to evaporating the water solution and subsequently extracting the solid with an organic solvent.

The hot benzene solution was filtered through a steam funnel and the filtrate was evaporated to dryness (5-liter flask in boiling water-bath). The air-dried residue of picolinic acid weighed 100 g. (38% yield). The residual solid in the extraction flask (picolinic acid

TABLE II

MELTING POINTS OF PICRATES OF RECOVERED PICOLINES

PICOLINES	AUTHENTIC PICOLINE PICRATES (A) M.P. (°C.)	PICRATES OF RECOVERED PICOLINES (B) M.P. (°C.)	MIXED PICRATES (A + B) M.P. (°C.)
2-Picoline	164–165	164–165	164–165
3-Picoline	147–149	146–148	146–148
4-Picoline	164–165	165–166	164–165

plus potassium chloride) was air-dried, screened to *ca.* 20 mesh, and re-extracted with 3000 cc. of benzene to give 66 g. of picolinic acid (25% yield); the combined yield was 166 g. (63%). (With 4.6 moles of permanganate instead of 5.7, the combined yield was 153 g.) The product titrated 99.8% pure and melted at 136.5–138°. Contrary to British patent 447,339 (1936) the picolinic acid contained little if any oxalic acid. The solubility of oxalic acid in boiling benzene (0.72 g. in 3000 cc.) fixed the maximal contamination at 1%, and mixed melting point determinations indicated that the contamination was less than 1%.

Four extraction residues were combined and the composite was twice extracted with benzene to give 32 g. and 12 g. of picolinic acid, respectively, raising the yield for a single oxidation to 177 g. (67% per-pass yield, 73% ultimate). The twice-extracted quadruple residue still contained 100 g. of picolinic acid. Therefore the ultimate oxidation efficiency was 83%. The picolinic acid in the residue can be concentrated by crystallization from water. For example, a residue containing 100 g. of picolinic acid and 1500 g. of potassium chloride was dissolved in 2800 cc. of boiling water, and the solution was cooled to 0°. Fifty per cent of the potassium chloride crystallized and the filtrate contained 99% of the picolinic acid.

(*B*) *Extraction by chloroform.* Boiling chloroform removed picolinic acid faster than benzene but yielded an impure product (*ca.* 93% pure) contaminated by potassium chloride. The solubility of picolinic acid in 1000 cc. of chloroform at 4, 33, and 64°, is 14, 31, and 81 g., respectively.

(*C*) *Liquid-liquid extraction.* Liquid-liquid extraction of aqueous picolinic acid at its

isoelectric point was fairly satisfactory. The efficiency of the extraction apparatus of Palkin, Murray, and Watkins (20) was raised by enlarging the extraction section and filling it with glass pearls to increase interfacial contact. Aqueous solutions (30 cc.) containing 9.3 g. of picolinic acid and an equivalent amount of potassium chloride (5.6 g.) were extracted at about 50° by benzene and chloroform (250 cc.). The recoveries of picolinic acid by benzene in 4, 11, and 35 hours were 23, 51, and 64%, respectively. The corresponding recoveries by chloroform in 4 and 11 hours were 83 and 89%, respectively. The 5.9 g. of picolinic acid extracted by benzene contained 0.05 g. of potassium chloride whereas the 8.3 g. of acid extracted by chloroform contained 1.2 g. of potassium chloride.

Nicotinic acid (*4–6, 8, 9, 15, 17, 21–25*). Two hundred grams (2.15 moles) of 3-picoline was oxidized in the same way as 2-picoline. The combined filtrate-wash was evaporated to 3000 cc. and the concentrate was set at *p*H 3.4 with about 260 cc. of concentrated hydrochloric acid. The mixture was heated to 95–100° to dissolve the voluminous precipitate and allowed to cool slowly to room temperature. The purpose of the slow cooling was to avoid contamination by potassium chloride. The nicotinic acid was washed with 50 cc. of cold water and air-dried. The filtrate was concentrated to 1300 cc., cooled at 5° overnight and filtered. The first crystal crop weighed 151 g. (air-dried 92% pure, pistol-dried 97.7% pure, 56% yield); the second crop weighed 61 g. (air-dried 83% pure, pistol-dried 91% pure, 21% yield). In all cases, air-drying took place at ordinary temperature and pressure, pistol-drying at reduced pressure (*ca.* 5 mm.) and 100°. The total per-pass yield of nicotinic acid was 77%; the ultimate yield was 83%. The solubility of nicotinic acid (crystallized from water, m.p. 234.5–235.5°, 99.6% pure) in 1000 cc. of water at 0, 40, 80, and 100°C, is 10, 26, 82, and 127 g., respectively.

Isonicotinic acid (*5, 6, 9, 18, 19, 22, 26–33*). 4-Picoline was processed as above, the precipitation *p*H being 3.6. Not all the precipitate dissolved when the mixture was heated to boiling. Slow cooling was employed as with nicotinic acid. The first crystal crop weighed 170 g. [air-dried 99.5% pure, pistol-dried 99.8% pure, m.p. 323–325° (dec.), 64% yield]. The second crystal crop weighed 17 g. (air-dried 94% pure, pistol-dried 94% pure, 6% yield). The total per-pass yield was 70%; the ultimate yield was 76%.

Crystallization of isonicotinic acid. Water is the best solvent for this purpose. The solubility of isonicotinic acid per 1000 cc. of water at 0, 40, 80, and 100° is 3, 9, 24, and 34 g., respectively. In water saturated with potassium chloride at 25° the solubility per 1000 cc. of solvent at 40, 68, and 100° is 8, 14, and 24 g., respectively.

Dipicolinic acid (*9, 10, 14, 15, 34–48*). 2,6-Lutidine (107 g., 1 mole) in 2500 cc. of water was oxidized by 838 g. of potassium permanganate (5.3 moles) added in ten portions during 17 hours. The concentrated filtrate-wash (2000 cc.) was made 1.5 normal with respect to hydrochloric acid by the addition of about 500 cc. of concentrated hydrochloric acid, heated to boiling to dissolve precipitated solid, allowed to cool slowly to room temperature, cooled overnight at 5° and filtered. The dipicolinic acid was washed with 50 cc. of cold water and air-dried. The filtrate was concentrated to 1200 cc., cooled at 5° overnight and filtered. The first crystal crop weighed 130 g. (air-dried 98% pure, pistol-dried 100% pure, 78% yield). The second crop was 8% pure (air-dried) and corresponded to an additional 6% yield; the impurity was potassium chloride. The total per-pass yield of dipicolinic acid was 84%; the ultimate yield was 92%. When 4.2 moles of permanganate was used instead of 5.3 moles, the per-pass yield was 57%, the first crop being 55% (air-dried 100% pure), the second crop 2% (air-dried 68% pure).

(*A*) *Method of precipitation.* It was essential that the acidified solution of dipicolinic acid be heated to boiling to dissolve all the solid, and that the hot solution be allowed to cool slowly, otherwise a gelatinous precipitate resulted which contained about 20% of potassium chloride. Potassium was determined as sulfate by ignition with sulfuric acid; chloride was determined as silver chloride, which was precipitated in 1.5 *N* nitric acid and filtered hot (*ca.* 65°).

Before the necessity of precipitation at high acidity was realized, the dipicolinic acid was usually contaminated with about 2.5% of potassium (negligible chloride) which cor-

responded to the presence of 7.8% of dipotassium dipicolinate or 13.2% of monopotassium dipicolinate. Pure dipicolinic acid could be obtained from this material by slow crystallization from water. The melting point of the acid was not much affected by this considerable salt contamination. The melting point of pure dipicolinic acid was 232–233° (dec., heating rate 1° per min.), whereas the melting point of impure dipicolinic acid containing 2.5% of potassium was 230–231° (dec.).

Dipicolinic acid can be recrystallized from 5 *N* hydrochloric acid, and the air-dried product is the free acid. The effect of hydrochloric acid normality on the solubility of dipicolinic acid is shown by solubility isotherms (Fig. 2). Relatively pure dipicolinic acid was sometimes obtained at *p*H 2.0, but the minimum acidity at which potassium-free acid was always obtained was *p*H 0.6.

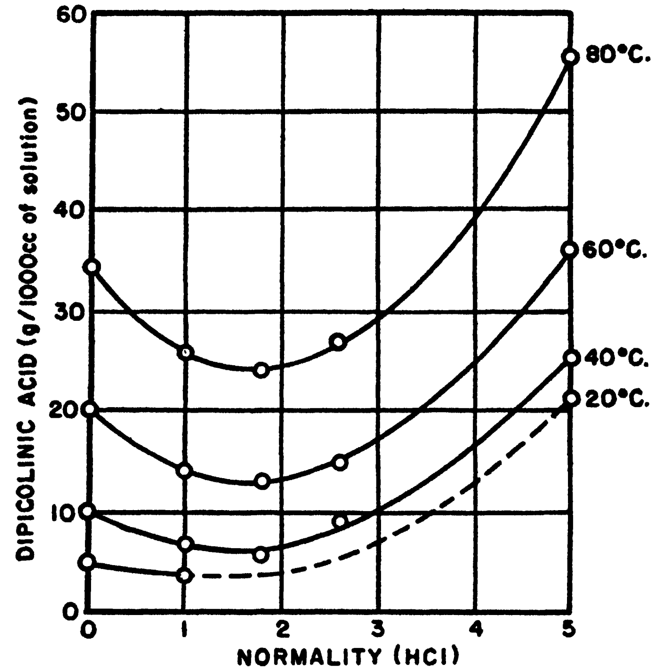

FIG. 2. SOLUBILITY ISOTHERMS OF DIPICOLINIC ACID

(*B*) *Potassium salts.* The calculated amount of potassium carbonate to form the monopotassium salt was added to an aqueous solution of dipicolinic acid. Short, thick crystals were obtained. This product was similar to one described by Pinner (9), who assigned the formula $C_7H_4NO_4K \cdot C_7H_5NO_4 \cdot 3H_2O$. Our air-dried product analyzed for $C_7H_4NO_4K \cdot C_7H_5NO_4 \cdot 2.5\ H_2O$.

Anal. Calc'd for $C_{14}H_{14}N_2O_{10.5}K$: K, 9.5; H_2O, 11.0.

Found: K, 9.4; H_2O, 10.8.

Fractional crystallization from water separated a product containing the theoretical amount of potassium for the monopotassium salt. The air-dried material was anhydrous.

Anal. Calc'd for $C_7H_4NO_4K$: K, 19.1. Found: K, 19.3.

6-Methylpicolinic acid (9, 47, 49–54). The oxidation was made as usual, except for temperature, starting with 107 g. (1 mole) of 2,6-lutidine and 335 g. (2.1 moles) of permanganate. The optimal temperature was 60–70° and the oxidation required 18 hours. Two methods of separating the mono- and di-acids were evaluated.

According to one method, the concentrated oxidation filtrate-wash (2500 cc.) was made 1.5 *N* with respect to hydrochloric acid whereupon dipicolinic acid crystallized on cooling. The mono-acid was subsequently recovered from the filtrate (set at *p*H 3.3) by dehydration-extraction with boiling benzene. The disadvantage of this method was the excessive quantity of potassium chloride produced by neutralizing the hydrochloric acid.

According to the other method, the oxidation filtrate-wash was concentrated to 500 cc., set at *p*H 3.3, and dehydrated-extracted by 1500 cc. of benzene. The mono-acid extracted by the dry benzene was free from di-acid. The solid in the extraction flask was extracted with 500 cc. of boiling 1.5 *N* hydrochloric acid, and dipicolinic acid crystallized from the solution on cooling.

These two methods of separation were based on the following solubility data. Dipicolinic acid is practically insoluble in boiling benzene (0.1 g. in 1000 cc.) and sparingly soluble in cold 1.5 *N* hydrochloric acid (Fig. 2), whereas the mono-acid is relatively soluble in benzene (9, 11, and 200 g. in 1000 cc. of benzene at 9, 20, and 80°, respectively), and very soluble in 1.5 *N* hydrochloric acid (8 g. per 10 cc. at 25°).

Using 60–70° as the oxidation temperature and the second method of separation, a 59% yield (80 g.) of 6-methylpicolinic acid and a 6% yield (10 g.) of dipicolinic acid was obtained. The former titrated 99% pure and melted at 126.5–128°.

Anal. Calc'd for $C_7H_7NO_2$: cc. of 0.1 *N* KOH, 20.7. Found: cc. of 0.1 *N* KOH, 20.6.

Upon exposure to air or crystallization from water, the anhydrous acid took on one molecule of water of crystallization and melted at 93.5–95°.

Anal. Calc'd for $C_7H_7NO_2 \cdot H_2O$: cc. of 0.1 *N* KOH, 17.5. Found: cc. of 0.1 *N* KOH, 17.6.

Isocinchomeronic acid (10, 36, 40, 41, 55–60). Numerous attempts were made to oxidize 2-methyl-5-ethylpyridine to the di-acid according to the procedure used for dipicolinic acid, but the results were erratic owing to the sluggishness with which the acid crystallized from the acidified concentrate of the oxidation filtrate, and the tenacity with which it retained potassium salt. An occasional 60% yield of acid (contaminated by 2% of potassium) was obtained by precipitating at *p*H 1 to *p*H 2.5. The finally accepted procedure was to make the dimethyl ester, from which potassium-free acid could be obtained. No attempt was made to develop procedures for preparing mono-acids from 2-methyl-5-ethylpyridine.

(*A*) *Dimethyl ester.* One mole of 2-methyl-5-ethylpyridine was oxidized by 7.9 moles of potassium permanganate in the usual manner. The combined filtrate-wash was concentrated and then dehydrated with benzene. The benzene was decanted, the dry solid was freed from benzene by evacuation, and to the solid was added a mixture of 700 g. of methyl alcohol and 910 g. of concentrated sulfuric acid. The solid-liquid mixture was refluxed in a water-bath for six hours with stirring, poured into cracked ice, and neutralized with aqueous sodium carbonate (about 900 g. of carbonate in 2500 cc. of water). The volume of solution was so chosen that solid dimethyl ester precipitated and sodium sulfate dissolved. The mixture was divided into two equal parts and each was vigorously stirred in a 5-liter flask with three portions of chloroform, 500 cc. the first time and 375 cc. the second and third times. The greater part of the chloroform solution separated after each extraction and the interfacial emulsion was broken by suction filtration. The combined extract (2500 cc.) was concentrated to about 400 cc. (*ca.* 65° liquid temperature), cooled in ice, and filtered. The small amount of mother liquor was allowed to evaporate at room temperature. The combined air-dried yield of the first and second crops (81.7 g. and 9.3 g., respectively) was 91 g. (46.5% yield). The crude ester melted at 161–163° and was 97% pure by saponification equivalent. Ester recrystallized from methanol melted at 162.5–163.5°. Its solubility in 1000 cc. of methanol at 3, 10, and 60° was 3, 10, and 40 g., respectively.

(*B*) *Hydrolysis of the dimethyl ester.* Dimethyl ester (19.5 g.) was refluxed for 4 hours with 100 cc. of 2 *N* hydrochloric acid; the mixture was cooled overnight at 5° and filtered to give 17.5 g. of isocinchomeronic acid (air-dried 93% pure, pistol-dried 99% pure, 95% yield). The anhydrous acid melted at 249–249.5° with decomposition [the 154° m.p. reported by

Meyer and Staffen (58) must be a typographical error]. Acid recrystallized from water and air-dried for a week contained 1.12 moles of water of crystallization, which it retained on subsequent exposure in an evacuated desiccator for 5 days (1 to 1.5 moles of water have been reported).

SUMMARY

Improved preparative directions are reported for picolinic, nicotinic, isonicotinic, dipicolinic, 6-methylpicolinic, and isocinchomeronic acids; also for dimethyl isocinchomeronate.

PITTSBURGH, 13, PA.

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[CONTRIBUTION No. 147 FROM THE RESEARCH LABORATORIES OF HOFFMANN-LA ROCHE, INC.]

THE REACTION OF L-ASCORBIC AND D-ISOASCORBIC ACID WITH NICOTINIC ACID AND ITS AMIDE

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L-Ascorbic acid, being a comparatively strong acid forms salts with organic amines such as Cinchona alkaloids (11), benzedrine (9), histidine (5), quinidine (3, 6), and aliphatic amines (2, 7, 10). All these compounds contain strongly basic amino groups. We became interested in the behavior of L-ascorbic acid toward weak cyclic organic bases while working on a synthesis of L-ascorbic acid by means of organic bases (12). These investigations were carried out during 1942. The results are published now because they extend the available knowledge in the literature.

It was found that L-ascorbic acid combines with nicotinamide to form a definite compound. Milhorat (8) described a color reaction of L-ascorbic acid and nicotinamide without isolating the compound. Its existence has since been reported by Bailey, Bright, and Jasper (1) and by Fox and Opferman (4), the former obtaining the compound by evaporation of solutions containing equimolecular amounts of the components, the latter by mixing the components in the dry state. Bailey, Bright, and Jasper also describe a compound consisting of nicotinic acid and L-ascorbic acid, made in a similar way. We prepared both compounds by crystallization from solvents. In addition we obtained a compound consisting of equimolecular amounts of D-isoascorbic acid and nicotinamide. The reactions between L-ascorbic acid and D-isoascorbic acid and these pyridine derivatives show some interesting features.

The reaction of L-ascorbic acid or D-isoascorbic with nicotinamide is a slow one. Its progress is visible because the newly formed compounds are yellow. The time required for the appearance of the yellow color varies with temperature, solvent etc., indicating that the reaction is not a mere salt formation which would take place immediately. In addition to the ordinary salt formation, there seems to be a further connection between L-ascorbic or D-isoascorbic acid and nicotinamide, probably of the nature of a secondary valence linkage. This assumption is supported by the optical properties of the new compounds. As is seen from Table I, the optical rotation of the complex differs considerably from that of the acid contained, with D-isoascorbic acid the rotation changing from levorotatory to dextrorotatory in the combination with nicotinamide.

Based on these findings we think it incorrect to name the new compounds "salts", and hence refer to the combination of L-ascorbic acid and nicotinamide as "nicotinamide-L-ascorbic acid complex" rather than calling it "nicotinamide L-ascorbate".

That mere salt formation is not sufficient explanation of the nature of the new compounds is still more evident from the behavior of L-ascorbic acid and D-isoascorbic acid toward free nicotinic acid. If free nicotinic acid possessing rather

weak basic properties is used as the base for "salt formation", only L-ascorbic acid reacts to form an addition product, whereas D-isoascorbic does not react. This is, to our knowledge, the sole reaction where L-ascorbic acid shows a distinct difference from D-isoascorbic acid in chemical behavior. The difference is so striking that it is useful for the differentiation between L-ascorbic and D-isoascorbic acid, and is suited for demonstration purposes. A 10–15% aqueous solution of L-ascorbic acid shaken for about 30 seconds with an equimolecular amount of nicotinic acid solidifies so that the flask can be turned upside down, whereas a corresponding solution of D-isoascorbic acid under the same conditions remains fluid, the nicotinic acid settles out, and is recovered unchanged by filtration.

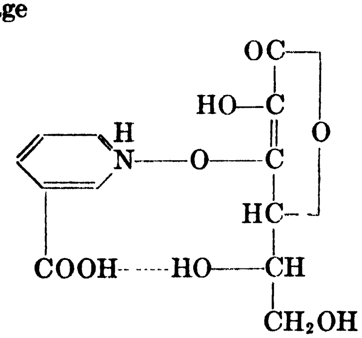
This difference in the formation of a complex cannot be explained by differences in acidity between L-ascorbic and D-isoascorbic acid, because both show practically the same *p*H in solutions. It seems logical to ascribe the difference in behavior to the difference in structure of both acids. Obviously the steric arrangement of the particular ascorbic acid is instrumental in bringing about the combination with nicotinic acid. This may be illustrated by a formula such as

TABLE I

OPTICAL ROTATION OF D-ISO- AND L-ASCORBIC ACID AND OF THEIR COMPLEXES WITH NICOTINAMIDE

COMPOUND	$[\alpha]_D^{25}$	DIFFERENCE
L-Ascorbic acid	+20.5°	6.6°
Nicotinamide-L-ascorbic acid	+27.1°	
D-Isoascorbic acid	−17.3°	30.4°
Nicotinamide-D-isoascorbic acid	+13.1°	

I for the nicotinic acid-L-ascorbic acid complex. The dotted line indicates a secondary valence linkage



I

between both components in addition to the salt type connection. In D-isoascorbic acid the steric arrangement of the secondary hydroxyl group may be such as to preclude formation of a complex. The formula I is of course not proved, but this or a similar spatial arrangement is undoubtedly responsible for the observed differences.

In nicotinamide the carbamyl group may, in contrast to the free carboxylic group in nicotinic acid, still possess enough affinity to allow a combination.

The underlying mechanism of the reaction between L-ascorbic acid and nicotinic acid may in some way be connected with the mechanism of antiscorbutic activity. If, in order to exert Vitamin C properties, the ene-diolic acids have first to undergo a combination with proteins, such a mechanism would explain why L-ascorbic acid is strongly antiscorbutic, whereas D-isoascorbic acid, being less able to form complexes, has a much weaker activity. It would be interesting therefore to compare antiscorbutic activity of the known isomers of L-ascorbic acid with their capacity to form complexes with compounds such as nicotinic acid.

EXPERIMENTAL

The melting points were taken with an uncalibrated set of Anschütz thermometers.

I. Nicotinamide-L-ascorbic Acid Complex

A. In abs. alcohol. Finely powdered L-ascorbic acid (17.6 g.) is added to a solution of 12.2 g. of nicotinamide in 100 ml. of abs. alcohol at 20°. The mixture is shaken by hand. After about 2 to 3 minutes it turns yellow, and the contents solidify. The cake is broken up, and the yellow crystals are filtered, washed with about 30 cc. of cold alcohol, and dried; yield 26–28 g., m.p. 144–145°.

B. In dilute alcohol. A solution of 17.6 g. of L-ascorbic acid in 20 cc. of water is prepared by warming to 70–80°. To this solution is added in one portion a cold solution of 12.2 g. of nicotinamide in 250 cc. of abs. alcohol. The mixture turns yellow. It is cooled immediately to 20–25°, whereupon crystallization starts rapidly. After cooling to 0° for several hours, the crystals are filtered; yield 19 g., m.p. 145–146°.

C. In methanol. Nicotinamide (12.2 g.) and L-ascorbic acid (17.6 g.) are suspended in methanol (100 ml.). On warming on the steam-bath, crystals form after a few seconds. The mixture is cooled after about 10 minutes to room temperature, the crystals are filtered and washed with ice cold methanol; yield 21 g., m.p. 146–147°.

D. In water. Nicotinamide (12.2 g.) and L-ascorbic acid (17.7 g.) are dissolved in water (100 ml.) by warming to 50–60°. As soon as solution is complete the mixture is cooled with ice-water. The complex starts to crystallize immediately. After cooling in the refrigerator for several hours, the crystals are filtered, washed with abs. alcohol and dried; yield 16 g., m.p. 145–146°. From the mother liquor additional amounts are obtained by concentration *in vacuo* and addition of alcohol.

E. Properties of the compound. Solubility: in water 0° approx. 10%, 20° approx. 40%, 80° more than 100%; in abs. alcohol 20° approx. 2.4%, 80° approx. 8%; in methanol 0° approx. 5%, 20° approx. 10%, 60° approx. 20%; in acetone sparingly soluble; in ether practically insoluble; in benzene practically insoluble. *Optical rotation:* $[\alpha]_D^{19.5}$ +27.1° (water, c, 4.97); $[\alpha]_D^{20.5}$ +27.6° (water, c, 8.46). *Acidity:* pH, 3.93 (water, c, 8.46); pH, 3.94 (water, c, 4.97); pH, 3.91 (alcohol, c, 2.40). *Titration:* 0.1988 g. used 12.65 cc. 0.1 *N* iodine; Calc'd 13.35 cc. 0.1 *N* iodine.

Anal. Calc'd for $C_{12}H_{14}N_2O_7$: C, 48.32; H, 4.73; N, 9.39.
Found: C, 48.38; H, 4.56; N, 9.58.

II. Nicotinamide-D-isoascorbic Acid Complex

A. In alcohol. Finely powdered D-isoascorbic (35.2 g.) is dissolved at 70–80° in abs. alcohol (300 ml.). To the hot solution a solution of nicotinamide (24.4 g.) in abs. alcohol (100 ml.) is added in one portion. The mixture is cooled. Yellow crystals separate. They are filtered, washed with abs. alcohol, and dried; yield 35 g., m.p. 129°.

B. In dioxane. A solution of 12.2 g. of nicotinamide in 50 ml. of dioxane at about 70–

80° is added to a suspension of 17.6 g. of D-isoascorbic in 50 ml. of dioxane, warmed to about 60° on a steam-bath. Everything dissolves, and after cooling, crystals separate. They are filtered, washed with cold dioxane and dried; yield 24 g., m.p. 128–129°.

C. Properties. Optical rotation: $[\alpha]_D^{21}$ +13.10° (water, c, 6.99); *Acidity:* pH, 3.8 (water, c, 5.2588); *Titration:* 0.1966 g. used 12.95 cc. 0.1 *N* iodine; Calc'd for $C_{12}H_{14}N_2O_7$ 13.19 cc. 0.1 *N* iodine.

Anal. Calc'd for $C_{12}H_{14}N_2O_7$: C, 48.32; H, 4.73; N, 9.39.
Found: C, 48.74; H, 4.67; N, 9.69.

III. Nicotinic Acid-L-ascorbic Acid Complex

A. In water. To a solution of 17.6 g. of L-ascorbic acid in 100 ml. of water, 12.3 g. of finely powdered nicotinic acid is added. The mixture is shaken. After about one minute it turns yellow and soon solidifies. About one hour later the crystals are filtered and washed with a little ice-water; yield 22 g., m.p. 185°.

B. In methanol. A solution of 17.6 g. of L-ascorbic acid in 100 ml. of boiling methanol is added to a suspension of 12.3 g. of finely powdered nicotinic acid in 50 ml. of methanol. The mixture is warmed on the steam-bath. After a few minutes the color changes to yellow, and shortly thereafter, the mixture solidifies to a compact maze of crystals. They are filtered, washed with ice-cold methanol, and dried; yield 27 g., m.p. 182–183°.

C. Properties of the compound. The combination between L-ascorbic acid and nicotinic acid is a rather loose one, as is apparent from the following behavior of the complex. The compound is not very soluble in cold water. Ten grams does not dissolve readily on shaking in 100 ml. of water at 20°. On warming solution occurs, but simultaneously the yellow color disappears. If a hot 10% solution is allowed to cool to about 40°, nicotinic acid separates in colorless crystals. It can be isolated practically free of L-ascorbic acid by filtration. However, if the solution is allowed to stand in the refrigerator, the complex re-forms, visible by the reappearance of the bright yellow color. Filtration of this cooled solution gives the complex.

From this behavior it follows that at temperatures above about 40° the complex is split into the components.

Solubility: water 26°: 3.3% (colorless solution); abs. alcohol 25°: slightly soluble; acetone: practically insoluble; (for comparison: solubility of L-ascorbic acid in water 25°: 33%; of nicotinic acid in water 25°: 1.8%). *Optical rotation:* $[\alpha]_D^{23}$ + 10.8° (water, c, 1.39). *Acidity:* *p*H = 3.4 (c, 0.806). *Titrations: I* 0.0701 g. used 4.39 ml. 0.1 *N* iodine; Calc'd for $C_{12}H_{13}NO_8$ 4.20 ml. 0.1 *N* iodine. *II* 0.1390 g. used 9.02 ml. 0.1 *N* NaOH; Calc'd for $C_{12}H_{13}NO_8$ 8.77 ml. 0.1 *N* NaOH. *Dissociation constant:* K = 0.00002; (nicotinic acid: K = 0.000014).

Anal. Calc'd for $C_{12}H_{13}NO_8$: C, 48.16; H, 4.38; N, 4.68.
Found: C, 48.94; H, 4.44; N, 5.08.

IV. D-Isoascorbic Acid and Nicotinic Acid

If in the experiments described under IIIA and IIIB, the L-ascorbic acid is replaced by D-isoascorbic acid, no reaction takes place. When such mixtures are filtered, a practically quantitative recovery of nicotinic acid is obtained.

Acknowledgment. The microanalyses reported in this paper were carried out in our Microchemical Laboratory under the direction of Dr. Al Steyermark.

SUMMARY

L-Ascorbic acid and D-isoascorbic acid combine with nicotinamide to form definite compounds.

Nicotinic acid forms such a compound with L-ascorbic acid, but not with D-isoascorbic acid.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NEW YORK UNIVERSITY, WASHINGTON SQUARE COLLEGE]

STUDIES IN DIARYLDIAMINOALKANEDIOLS

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In continuation of previous investigations in the field of adrenaline-like compounds (1), it was thought desirable to commence on a program of synthesizing diaryldiaminoalkanediols. In the present paper the first attempts in this field are given, involving the preparation of diphenylethylamine types and diadrenaline types.

The preparation of both types of these compounds involved the following simple reaction scheme:

$$\mathrm{ArCOCH_2}\boxed{\mathrm{X + H}}\mathrm{NH(CH_2)_nNH}\boxed{\mathrm{H + X}}\mathrm{CH_2COAr} \xrightarrow[\mathrm{EtOH}]{\mathrm{K_2CO_3}}$$

$$\mathrm{ArCOCH_2NH(CH_2)_nNHCH_2COAr} \xrightarrow[\mathrm{Pd}]{\text{reduction}}$$

$$\mathrm{ArCHOHCH_2NH(CH_2)_nNHCH_2CHOHAr}$$

$$\mathrm{Ar} = \mathrm{C_6H_5}—,\ \mathrm{(HO)_2C_6H_3}—. \quad n = 2, 3 \text{ or } 5. \quad \mathrm{X} = \mathrm{Cl} \text{ or } \mathrm{Br}$$

According to the above, unsubstituted phenacyl bromide was treated with half-molar equivalent quantities of a diamine (ethylene-, trimethylene- and pentamethylene-), to yield the corresponding N,N′-diphenacyldiamines, which were then reduced to the corresponding secondary amino alcohols. In the diadrenaline series, instead of the unsubstituted phenacyl bromide, the 3,4-dihydroxyphenacyl chloride was used, which was prepared by rearranging catechol chloroacetate (2), in the conventional manner (3).

EXPERIMENTAL

Aminations. N,N′-Diphenacylethylenediamine dihydrochloride. To phenacyl bromide 6.6 g. (0.033 mole) dissolved in 20 cc. of absolute alcohol, 2.0 g. (0.033 mole) of anhydrous ethylenediamine was added drop by drop while shaking the flask in an ice-bath. After the addition was complete, the flask was shaken for five more minutes and allowed to stand for one more hour. In the mean time the dihydrobromide of the excess ethylenediamine precipitated out. This was filtered and the precipitate was washed twice with 5-cc. portions of absolute alcohol. Dry hydrochloric acid gas was passed into the filtrate for five minutes, when the solution became bluish green, and to this solution 30 cc. of anhydrous ether was added to precipitate the amine as a hydrochloride salt. After keeping this in the refrigerator overnight, it was filtered on a Jena crucible and the precipitate was washed four times with 5-cc. portions of absolute alcohol. The white residue was washed with 5 cc. of cold distilled water to remove any last traces of ethylenediamine hydrochloride present. The final product was then recrystallized from dilute alcohol.

When the reactants were refluxed for one hour on a water-bath, a pale yellow residue, insoluble in both alcohol and water, remained on the filter paper after washing off the

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ethylenediamine hydrobromide precipitate obtained from the original reaction mixture. This substance was purified by dissolving in 5 cc. of alcohol containing 2 cc. of concentrated hydrochloric acid and reprecipitating by making it just alkaline with ammonium hydroxide. It was found by analysis to be N,N,N',N'-tetraphenacylethylenediamine.

TABLE I

DIPHENYLETHYLAMINE COMPOUNDS

NAME	FORMULA	M.P.; °C. (UNCOR.)	NITROGEN, %	
			Calc'd	Found
N,N'-Diphenacylethylenediamine:				
Free amine	$C_{18}H_{20}N_2O_2$	105–109 (darkens)	9.47	9.18
Dihydrochloride	$C_{18}H_{22}Cl_2N_2O_2$	258–259	7.59	7.45
Disulfate	$C_{18}H_{24}N_2O_{10}S_2$	252–253	5.70	5.52
N-Benzoyl(mono)deriv.	$C_{24}H_{24}N_2O_3$	233–234	7.10	7.29
N,N'-Di(phenylethanol)ethylenediamine:				
Dihydrochloride	$C_{18}H_{26}Cl_2N_2O_2$	290–292d	7.50	7.24
N,N'-Diphenacyltrimethylenediamine:				
Free amine	$C_{19}H_{22}N_2O_2$	120–122	9.03	8.72
Dihydrochloride	$C_{19}H_{24}Cl_2N_2O_2$	250–251	7.31	7.20
Disulfate	$C_{19}H_{26}N_2O_{10}S_2$	204–205	5.52	5.51
N,N'-Di(phenylethanol)trimethylenediamine:				
Dihydrochloride	$C_{19}H_{28}Cl_2N_2O_2$	237–238	7.23	7.45
N,N'-Diphenacylpentamethylenediamine:				
Free amine	$C_{21}H_{26}N_2O_2$	115–117	8.38	8.02
Dihydrochloride	$C_{21}H_{28}Cl_2N_2O_2$	253–254	6.81	6.70
Disulfate	$C_{21}H_{30}N_2O_{10}S_2$	222–223	5.24	5.47
N,N'-Di(phenylethanol)pentamethylenediamine:				
Free amine	$C_{21}H_{30}N_2O_2$	103–104	8.18	7.92
Dihydrochloride	$C_{21}H_{32}Cl_2N_2O_2$	240–241	6.74	7.02

TABLE II

TETRAPHENYLETHYLAMINE COMPOUNDS

NAME	FORMULA	M.P.; °C. (UNCOR.)	NITROGEN, %	
			Calc'd	Found
N,N,N',N'-Tetraphenacylethylenediamine:				
Free amine	$C_{34}H_{32}N_2O_4$	196–198	5.26	5.47
Dihydrochloride	$C_{34}H_{34}Cl_2N_2O_4$	131–133d	4.66	4.77
Picrate(mono)	$C_{40}H_{35}N_5O_{11}$	168–169	10.27	9.90
N,N,N',N'-Tetra(phenylethanol)ethylenediamine:				
Free amine	$C_{34}H_{40}N_2O_4$	165–169d	5.18	4.97
Dihydrochloride	$C_{34}H_{42}Cl_2N_2O_4$	124–126d	4.56	4.48

N,N'-Diphenacyl tri- and penta- methylenediamine dihydrochlorides. To phenacyl bromide 7.8 g. (0.04 mole), dissolved in 20 cc. of absolute alcohol, 4.0 g. of potassium carbonate (anhydrous) and 1.6 g. (0.02 mole) of trimethylenediamine (4) [2.0 g. (0.02 mole) in case of pentamethylenediamine] were added and refluxed on a water-bath for two hours. After

keeping the reaction mixture at room temperature overnight, it was filtered and the precipitate was washed twice with 5-cc. portions of absolute alcohol, and with 5-cc. portions of cold distilled water to remove the excess potassium carbonate and potassium bromide. The residue along with the filter paper, was treated with 20 cc. of hot alcohol containing 2 cc. of concentrated hydrochloric acid and filtered while hot. On cooling, glistening plates were obtained. More of these hydrochloride crystals were obtained by passing dry hydrochloric acid gas into the alcoholic filtrate from the original reaction mixture for five minutes and keeping it overnight with the addition of 30 cc. of anhydrous ether.

Free amines. The alcoholic-ether filtrates, after filtering off the hydrochloride salts, were allowed to evaporate to dryness at room temperature. The residues thus obtained were then treated with 50 cc. of hot water (80°) and filtered The cooled filtrates were made alkaline to litmus with ammonium hydroxide and were filtered after cooling in an ice-bath for one hour. The free amines thus obtained were purified by reprecipitating two more times after dissolving in 50 cc. of hot hydrochloric acid and neutralizing with ammonium hydroxide. Total yields: ethylenediamine, 22%; trimethylenediamine, 31%; pentamethylenediamine, 29%.

TABLE III

DIADRENALONE AND RELATED COMPOUNDS

NAME	FORMULA	M.P., °C. (UNCOR.)	NITROGEN, %	
			Calc'd	Found
N,N′-Di(3,4-dihydroxyphenacyl)ethylenediamine (Diadrenalone):				
Free amine	$C_{18}H_{20}N_2O_6$	About 210 (softens)	7.78	7.92
N,N′-Di(3,4-dihydroxyphenacyl)trimethylenediamine:				
Free amine	$C_{19}H_{22}N_2O_6$	About 200 (darkens)	7.48	7.64
N,N′-Di(3,4-dihydroxyphenacyl)pentamethylenediamine:				
Free amine	$C_{21}H_{26}N_2O_6$	About 225 (softens)	6.96	6.83
Dihydrochloride	$C_{21}H_{28}Cl_2N_2O_6$	258–260	5.89	6.22

Disulfates were obtained by treating the hydrochloride salts with alcohol and concentrated sulfuric acid and heating until the solution became clear After filtering while hot and upon cooling, the disulfate salts were precipitated out

N,N′-Di(3,4-dihydroxyphenacyl) ethylene-, trimethylene- and pentamethylenediamines. In a three-neck flask (250 cc.), fitted with a mercury sealed stirrer, a reflux condenser, and a delivery tube, 50 cc. of alcoholic solution containing 12.5 g. (0.066 mole) of 3,4-dihydroxyphenacyl chloride was mixed with 4.0 g. (0.066 mole) of ethylenediamine (5.0 g. of trimethylenediamine and 6.8 g. of pentamethylenediamine respectively). Immediately a yellow, finely grained precipitate of the addition product separated out. While passing nitrogen through the reaction mixture and stirring it vigorously, it was heated on a water-bath for one hour and a half. To the dark brown reaction mixture, 15 cc. of concentrated hydrochloric acid was added. After cooling, it was filtered and to the filtrate ammonium hydroxide was added drop by drop until a dark brown precipitate was obtained. This was filtered and rejected as an impurity. Addition of some more ammonium hydroxide to the filtrate until it was just alkaline to litmus yielded the free amine. This was filtered, washed with water and dried *in vacuo*. Total yields: ethylenediamine, 34%; trimethylenediamine, 55%; pentamethylenediamine, 32%.

In the case of pentamethylenediamine, when the reaction mixture was filtered, 0.5 g. of reaction product remained on the filter paper. This was dissolved in 5 cc. of hot distilled water (80°), decolorized with carbon, and filtered. To the filtrate 20 cc. of concentrated hydrochloric acid was added, and the reaction mixture kept in cold water overnight, thus hastening precipitation of N,N'-di(3,4-dihydroxyphenacyl)pentamethylene dihydrochloride.

Reduction. Half a gram of keto-amine hydrochloride was dissolved in 20 cc. of hot distilled water and 0.1 g. of palladium-charcoal catalyst (5) was added. The mixture was shaken in a hydrogenator under 45 pounds pressure at room temperature for two hours. The used catalyst was filtered off and the filtrate was evaporated to dryness. The residue was dissolved in 20 cc. of hot absolute alcohol and reprecipitated by adding 20 cc. of anhydrous ether.

SUMMARY

In the course of systematic studies in the preparation of diaryldiaminoalkanediols, a series of diphenylethylamine and diadrenaline types of compounds were prepared. The new compounds were properly characterized and derivatized. The physiological properties of these new compounds are under investigation.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

THE PREPARATION OF CYCLOBUTANE

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Although Willstätter and Bruce (1) prepared cyclobutane as early as 1907 this hydrocarbon has remained so difficultly accessible that accumulation of physical data concerning it has lagged behind that available for the other low molecular weight cycloalkanes. In order to supply material for further study of cyclobutane in this laboratory[1] we have undertaken the development of improved methods for its preparation.

Since cyclopropane is easily prepared in high yield (2) by the Wurtz reaction on trimethylene bromide, it might be expected that cyclobutane could be readily prepared from tetramethylene bromide. Demjanow (3) has reported, however, that the Wurtz reaction on tetramethylene bromide, using zinc in ethanol, leads to *n*-butyl bromide, while Hamonet (4) obtained *n*-butane. Recently, Keilin (5) has studied this reaction under a variety of conditions, including those found best for preparation of cyclopropane, and obtained no cyclobutane under any conditions used. The product was either butane or a mixture of butane and unsaturated material.

The original successful synthesis of Willstätter (1, 6) utilized cyclobutanecarboxylic acid as starting material. This acid was converted to the amide which was in turn converted to cyclobutylamine by the Hoffman hypohalite reaction. Exhaustive methylation and pyrolysis of the quaternary hydroxide gave cyclobutene mixed with 1,3-butadiene. Bromination of this mixture was followed by separation of the bromides, and cyclobutene was regenerated from the dibromide. Careful hydrogenation gave cyclobutane. This lengthy procedure was necessary for elimination of the carboxyl group, for Perkin and Colman (7) had found that decarboxylation by heating the calcium salt gives ethylene.[2] Although Willstätter's method starts with a relatively inaccessible material and gives a very low over-all yield, it has remained the principal source of cyclobutane. Heisig (8) has been able to improve the yield by using the Curtius acid azide rearrangement for preparation of the amine. The only other method which has yielded any cyclobutane is photolysis of cyclopentanone (9), and this process seems hardly practical for production of appreciable amounts of the hydrocarbon. The elaborate apparatus described in the patent was claimed to produce about 0.001 mole of cyclobutane per hour.

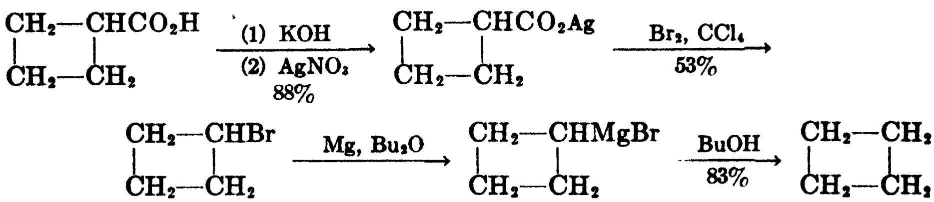
The present investigation was first directed towards the Wurtz reaction on tetramethylene bromide, and it has been found that when this reaction is carried

[1] These investigations will be reported in another journal by Professor K. S. Pitzer and co-workers.

[2] In an experiment by Mr. Donald Orth, of this laboratory, it was found that decarboxylation with copper chromite in boiling quinoline also leads to no products condensable at −70°. The evolved gases gave a precipitate with barium hydroxide and reduced permanganate.

out with sodium in boiling toluene a 7% yield of cyclobutane may be obtained. There was also obtained a similar amount of butane, which boils only about 12° below cyclobutane, and the necessity for separating this mixture detracts from the utility of the method. Since unsaturation tests on the butane fraction were negative it would appear that protons for reduction to butane must have been obtained from the solvent; so the reaction was run in benzene, in hopes that butane formation would be reduced by the lesser tendency of benzene to donate protons. Unfortunately, a contrary result was obtained; the yield of cyclobutane became nearly zero even when the concentrations in benzene were reduced to one-fourth those used in toluene. This difference might be ascribed to the fact that sodium is solid in boiling benzene and molten in boiling toluene; however, it seems more probable that the temperature coefficient of the reaction leading to cyclobutane is greater than those of competing reactions leading to other products. The reaction has not been studied in higher-boiling solvents, for at this stage of the investigation there was developed the method described below, which yields cyclobutane free of butane.

Pure cyclobutane may be obtained in quantities of a mole or more by the illustrated sequence of reactions.



The over-all yield from cyclobutanecarboxylic acid is about 39%. Preparation of this starting material has been studied and will be reported in a later publication.

The reaction of a silver salt with bromine in anhydrous medium, as developed by Hunsdiecker (10) and applied to numerous compounds (11), was successful with silver cyclobutanecarboxylate after proper conditions had been discovered. When the reaction was carried out by adding bromine to a suspension of the silver salt in boiling carbon tetrachloride, no cyclobutyl bromide could be isolated. The entire product consisted of higher-boiling material. When the reaction was carried out by adding the silver salt to a carbon tetrachloride solution of bromine at −25°, considerable high-boiling material was again obtained, but there was also isolated the indicated yield of cyclobutyl bromide, b.p. 108.2–108.3° (760 mm.).

The high-boiling material from both the lower and higher temperature reactions was found to consist of two fractions. The lower-boiling of the two fractions proved to be cyclobutyl cyclobutanecarboxylate, the ester which would result from reaction of the silver salt with cyclobutyl bromide. Such an ester is a recognized by-product of the silver salt reaction with one molar equivalent of bromine, but in the other instances studied the ester has been obtained in smaller amount. The larger amount of ester obtained in the present instance may be a

result of the bromide being secondary, but it may also be a result of the fact that the intermediate in the reaction (presumably RCO_2Br, *cf.* ref. 11) lost carbon dioxide readily, even at −25°, after a short induction period. Thus, bromide was present as the last of the silver salt was added, and there was opportunity for the two to react. There is no proof, however, that the ester is formed by this mechanism. It may be formed by way of a different complex between the silver salt and bromine (11).

The higher-boiling by-product, present in smaller amount in the low-temperature reaction, proved to be of high density and to contain bromine.[3] The analysis and molecular refraction are in reasonable agreement with the formula, $C_4H_7Br_3$; hence, the four-carbon ring appears to have been opened by bromine unless there was prior rearrangement to a three-carbon ring. Determination of the structure of the tribromide should throw some light on this matter, but it has not been further investigated by us since our present objective is preparation of cyclobutane.

Conversion of cyclobutyl bromide to the hydrocarbon by way of the Grignard reagent offered no difficulties when the reaction was run in di-*n*-butyl ether, and the Grignard complex was decomposed with *n*-butyl alcohol. Use of these reagents permitted easy separation of the low-boiling product, which was passed through a sulfuric acid wash and collected in a cold trap. Distillation through a four-foot column showed the condensate to consist almost entirely of cyclobutane, b.p. 11.15–11.35° (760 mm.)

EXPERIMENTAL

Microanalyses are by C. W. Koch and V. H. Tashinian. Boiling points are corrected with an accuracy of about 0.3°. Reduced pressures of 5 mm. or more were measured with a Zimmerli gage, those less than 5 mm. were measured with a tilting McLeod gage.

Cyclobutyl bromide. A mixture of 100 g. (1 mole) of cyclobutanecarboxylic acid and 270 ml. of water was titrated to a phenolphthalein end-point with 2 *N* potassium hydroxide. This solution was stirred vigorously while a solution of 172 g. (1.01 mole) of silver nitrate in 540 ml. of water was added during ten to fifteen minutes. The thick mixture was stirred an additional fifteen minutes, then the silver cyclobutanecarboxylate was collected by suction filtration. The salt was stirred well with 800 ml. of water, collected again, and washed with methanol. After drying overnight at atmospheric pressure at about 100°, the salt was ground, dried overnight in a vacuum oven at 95–100° (wt. 181.5 g., 87.7% yield), placed in the flask in which it was used for the next reaction, and again dried overnight in the vacuum oven at 95–100°.

To a flask equipped with mercury-sealed stirrer was added 560 ml. of carbon tetrachloride (dried over phosphorus pentoxide), and 50 ml. of carbon tetrachloride was distilled in order to dry the flask thoroughly utilizing the azeotrope with water. The system was protected with a drying tube, and after addition of 85.2 g. (0.534 mole) of bromine (dried over phosphorus pentoxide), the mixture was cooled to −25° with stirring. The silver salt (111 g., 0.534 mole) was added during about fifty minutes through a wide rubber connection from the flask in which it had been dried. After an induction period of five to twenty minutes vigorous evolution of carbon dioxide set in, and continued as the remainder of the silver salt

[3] Prior to our isolation of this compound, it was isolated in the laboratory of Professor E. R. Buchman, at California Institute of Technology. Our high-boiling fractions were worked up after Professor Buchman had advised us in a private communication that they had obtained the tribromide as a chief product of the reaction.

was added. Evolution of carbon dioxide was accompanied by evolution of heat, but the temperature was easily maintained at −25 to −20° with a Dry-Ice-acetone bath. After addition was complete the mixture was stirred an additional brief period until gas evolution became slow, then was allowed to warm to room temperature with stirring. When gas evolution had ceased, the silver bromide was removed and washed with carbon tetrachloride. The filtrate was washed with 2 N sodium hydroxide and water, then dried over calcium chloride. The combined alkaline extracts from a total of 2.6 moles of silver salt yielded only 2.2 g. of acidic material.

The carbon tetrachloride solution was flash-distilled through a 1-meter column packed with glass helices and equipped with heated jacket and partial reflux head. During flash distillation, the mole fraction of cyclobutyl bromide in the pot was kept below 0.2, and carbon tetrachloride was collected at 76.9°. After addition was complete, removal of solvent was continued, then an intermediate fraction was collected, b.p. 76.9–108.2°, wt. 7.9 g. Cyclobutyl bromide was collected at 108.2–108.3° (760 mm.), n_D^{20} 1.4801, d^{20} 1.434, MR_D^{20} 26.75 (calc'd 26.72). The weight of this fraction was 36.0 g. (50%), and there was 15.0 g. of distillation residue. By redistilling the intermediate fractions from several runs, and stripping the residues in a vacuum, the total yield was raised to 53%. The same yield was obtained in a 1.9-mole run. Perkin (12) reported the b.p. of cyclobutyl bromide as 104°.

By-products from cyclobutyl bromide preparation. The distillation residues from three runs in which a total of 2.6 moles of silver salt was processed were distilled in a vacuum to yield the following fractions: (a) wt. 9.0 g., b.p. 34.0–35.0° (50 mm.); (b) 4.8 g., b.p. 35.0° (50 mm.) −88.0° (16 mm.); (c) 25.3 g., b.p. 88.0–90.5° (16 mm.); (d) 1.3 g., b.p. 67.5–94.0° (5 mm.); (e) 16.7 g., b.p. 94.0–96.0° (5 mm.); residue 8.9 g. Fraction (a) is cyclobutyl bromide, while fractions (b) and (d) are intermediate fractions. Fraction (c) is *cyclobutyl cyclobutanecarboxylate*, and for analysis there was used a center cut of this fraction, b.p. 89.0–89.1° (16 mm.) n_D^{20} 1.4542, d^{20} 0.995.

Anal. Calc'd for $C_9H_{14}O_2$: C, 70.10; H, 9.15; MR, 41.98.
Found: C, 69.80; H, 9.11; MR_D^{20}, 41.96.

Fraction (e) is the *tribromobutane* first obtained by Buchman. For analysis there was used a center cut, b.p. 76.0–76.3° (1.9 mm.), n_D^{21} 1.5606, d^{21} 2.124.

Anal. Calc'd for $C_4H_7Br_3$: C, 16.30; H, 2.38; Br, 81.31; MR, 44.05.
Found: C, 18.10, 18.12; H, 2.70, 2.83; Br. 78.18; MR_D^{21}, 44.00.

Although the tribromide boiled over a narrow range, and refractionation failed to indicate constituents of different boiling point, "streaming effect" was noted in the receiver throughout distillation of this fraction, and the elementary analysis showed the presence of a small amount of a substance containing much less bromine and some oxygen. This was probably cyclobutyl 1-bromocyclobutane-1-carboxylate.

From a run in which the bromine was added to a stirred suspension of the silver salt in boiling carbon tetrachloride, no cyclobutyl bromide was obtained. The high-boiling product contained a ratio of 3.1 g. of ester to 4.0 g. of tribromide.

Cyclobutane. (A) *From tetramethylene bromide.* To 100 g. (4.35 atoms) of sodium, stirred vigorously under 465 ml. of dry, sulfur-free toluene, heated to boiling, there was added during ninety minutes 280 g. (1.3 mole) of tetramethylene bromide. The toluene was kept boiling, and the reaction was carried out in an atmosphere of nitrogen. Evolved gases which passed a water-cooled condenser were bubbled through concentrated sulfuric acid and collected in a trap cooled with Dry Ice and acetone. The trap was protected by a drying tube, and the system was thoroughly dried in a stream of nitrogen before the reaction was started. After bromide addition was complete, the reaction mixture was heated under reflux until gas evolution ceased (about thirty minutes). The material collected in the cold trap (13.3 g.) was fractionally distilled through a 4-foot vacuum-jacketed column[4]

[4] We are indebted to Professor K. S. Pitzer for the use of this column, which was constructed in his laboratory, and to Mr. A. Webb for assistance in its operation. The boiling

consisting of a 6 mm. tube, and equipped with partial reflux head and vapor take-off. The following fractions were obtained at 760 mm. pressure: (a) n-butane, wt. 4.7 g., b.p. −2.0–0.0°; (b) intermediate, wt. 2.5 g., b.p. 0.0–9.0°; (c) cyclobutane, wt. 5.1 g., b.p. 9.0–12.0°; residue, 1.0 g. The yield of cyclobutane was 7%, and a center cut obtained on redistillation, wt., 2.2 g., b.p. 11.0–11.3°, gave an infra-red spectrum[1] nearly identical with that shown by the sample described below. A b.p. of 12.5° (760 mm.) is calculated from Heisig's (8) vapor pressure data.

When an identical reaction was carried out in boiling benzene, after the sodium had been powdered under toluene, there was obtained from one mole of tetramethylene bromide only 5.4 g. of material in the cold trap, and fractional distillation gave 2.2 g. of fore-run, 2.2 g. of cyclobutane, b.p. 8.8–11.1°, and 1.0 g. of residue.

When a third run was made, using four times the volume of benzene used in the previous run, only 3.0 g. of material was collected in the cold trap, and there was no fraction boiling above 10.5°. Since it was felt possible that there was some difficulty in separating the cyclobutane from the benzene by simply heating under reflux, excess sodium was destroyed with methanol and the mixture was heated under a 3-foot packed column until benzene reached the top of the column, but no further gas was evolved.

(B) *From cyclobutyl bromide.* A flask arranged for carrying out a Grignard reaction in an atmosphere of nitrogen was attached to a gas absorption train similar to that described above, and in the flask were placed 100 ml. of absolute di-n-butyl ether,[5] 4.86 g. of magnesium turnings, and 2 g. of cyclobutyl bromide. After the reaction had been started by stirring the mixture for a few minutes at about 50°, there was added during two hours a solution of 24.9 g. of cyclobutyl bromide in 100 ml. of absolute di-n-butyl ether, the temperature being maintained at 40–50°. After addition was complete, the mixture was stirred an additional fifteen minutes, then treated with 40 ml. of n-butyl alcohol during about thirty minutes while the temperature was kept below 50° by external cooling. The homogeneous stirred mixture was then slowly warmed under reflux at such a rate that none of the evolved gas passed the cold trap, and the solution was finally heated to boiling until no more gas was evolved (total heating time about ninety minutes). Fractionation of the condensed gas through the 4-foot column gave 0.8 g. of fore-run, b.p. 5.5–11.00°, and 9.3 g. (83% yield) of cyclobutane, b.p. 11.0–11.35°.

From a similar run using 1.2 mole of cyclobutyl bromide, there was obtained 2.4 g. of fore-run, b.p. 8.5–11.15°, and 49.5 g. (77% yield) of cyclobutane, b.p. 11.15–11.35°.

SUMMARY

There has been developed a new method for preparing cyclobutane from cyclobutanecarboxylic acid. Silver cyclobutanecarboxylate was converted to cyclobutyl bromide, which was in turn converted to cyclobutane by way of the Grignard reagent.

Cyclobutane has also been obtained in 7% yield by means of the Wurtz reaction on tetramethylene bromide.

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point was measured with a thermocouple inserted in a glass well containing oil, which was inside the cooling head; so the b.p.'s reported for the low-temperature distillations may be somewhat low.

[5] Di-n-butyl ether appears to form an azeotrope with n-butyl alcohol, for a sample of the ether which had been distilled through a half-meter column and collected over a range of 0.5° contained considerable quantities of alcohol. Evolution of gas ceased only after standing over sodium for several weeks. This behavior is not explained by any reported azeotrope of di-n-butyl ether [Horsley, *Anal. Chem.*, **19**, 508 (1947)].

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[Contribution from the Chemical Laboratory of the University of California]

A CONVENIENT PREPARATION OF SUBERIC ACID. CONCERNING THE HOMOGENEITY AND USE IN SYNTHESIS OF POLYMETHYLENE CHLOROBROMIDE PREPARATIONS

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The dibasic acids have a variety of uses in synthesis, and have proved very valuable for extending the carbon chain in synthesis of branched-chain fatty acids, either by use of organocadmium reagents (1) or by acylation of β-keto esters (2). All the normal dibasic acids with ten or less carbons have been easily available, except for pimelic acid and suberic acid. Until recently, pimelic acid was obtained only by relatively tedious syntheses (3), but this acid is now easily obtained in high over-all yield from tetrahydropyran,[1] proceeding by way of the pentamethylene dihalide and the corresponding dinitrile. These reactions have been reported in the literature, but somewhat simplified experimental procedures are described in this paper.

A pentamethylene dihalide from tetrahydropyran may also serve as starting material for preparation of suberic acid, proceeding by way of the illustrated sequence of reactions.

$$Br{-}(CH_2)_5{-}Br \;+\; \underset{(1.2\text{ equiv.})}{KCN} \;\rightarrow\; \underset{(26\%\text{ yield})}{Br{-}(CH_2)_5{-}CN} \;+\; \underset{(27\%\text{ yield})}{NC{-}(CH_2)_5{-}CN}$$

$$\begin{array}{l} CO_2C_2H_5 \\ | \\ CH^{+} \\ | \\ CO_2C_2H_5 \end{array} \;+\; Br{-}(CH_2)_5{-}CN \xrightarrow{81\%}$$

$$\begin{array}{l} CO_2C_2H_5 \\ | \\ CH{-}(CH_2)_5{-}CN \\ | \\ CO_2C_2H_5 \end{array} \xrightarrow[\substack{(2)\ -CO_2 \\ 95\%}]{(1)\ H_2O,\ H^{+}} \begin{array}{l} CO_2H \\ | \\ (CH_2)_6 \\ | \\ CO_2H \end{array}$$

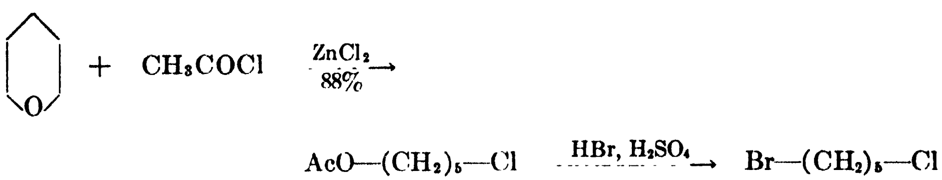
This sequence of reactions proceeds more favorably when pentamethylene dichloride[1] is used as starting material, if a small amount of potassium iodide is used as catalyst in each of the first two reactions. The alkyl chloride is converted to the more reactive iodide, and on reaction of the iodide with the other component the iodide ion is regenerated for further use in the same sequence of reactions. Using only four mole per cent of potassium iodide, the metathesis with cyanide proceeded as rapidly with pentamethylene dichloride as when pentamethylene dibromide was used. Alkylation of malonic ester with ω-chlorocapronitrile was complete in four hours when twenty-five mole per cent of

[1] We are indebted to the Electrochemicals Division, E. I. du Pont de Nemours and Co., for supplying us with the tetrahydropyran and pentamethylene dichloride used in this investigation.

potassium iodide was used. The dichloride has the advantage that the yield of halonitrile is appreciably greater than when the dibromide is used. Using 1.2 equivalent of potassium cyanide, there was obtained 37% yield of chloronitrile and 20% yield of dinitrile.

It is seen that the only poor yield in this process is in the first step, and this is offset by recovery of nearly 20% of the starting material and by the usefulness of pentamethylene dicyanide for making pimelic acid. If the yield in the first step is based on dichloride consumed the over-all yield of suberic acid from pentamethylene dichloride is about 35%. If desired, the ratio of recovered dichloride to dicyanide may be increased by reducing the equivalency of potassium cyanide to 1.1. This has only a small effect on the yield of halonitrile. Increasing the equivalency of potassium cyanide above about 1.2 lowers the yield of halonitrile.

Since the most attractive method for improving the yield of ω-halocapronitrile would seem to be its preparation from pentamethylene chlorobromide, this dihalide was prepared from tetrahydropyran by the following route:



Cyclic ethers have been opened with acetyl chloride by several investigators (1, 4), and the preparation of ω-acetoxyamyl chloride has recently been reported by Synerholm (5). A complication was encountered in the second step of this procedure, in that chlorine is replaced by bromine at an appreciable rate when the alkyl chloride is heated with hydrobromic and sulfuric acids. Table I shows the composition of the products obtained when 0.25 mole of ω-acetoxyamyl chloride was heated for various lengths of time with 0.5 mole of sulfuric acid and 0.5 mole of 48% hydrobromic acid. The figures in the fourth column represent the percentage of the total yield which was the chlorobromide, the remainder being dibromide. The last column gives the yield of chlorobromide, based on acetoxy chloride. Since the actual yield of chlorobromide remains constant from fifteen minutes up to two hours, it follows that conversion of chlorobromide to dibromide is compensated by conversion of acetoxy chloride to chlorobromide.

Composition of the mixture was determined by use of the specific gravity, after the specific gravities of pure pentamethylene dibromide and pure pentamethylene chlorobromide had been determined. By determining the values for known mixtures it was shown that linear extrapolation between these values is subject to less than 1% error. The validity of the analysis of reaction mixtures was also established by separating one reaction mixture by fractional distillation. A trace of pentamethylene dichloride was present, and the composition of small intermediate fractions was estimated, but the composition obtained by fractionation was within 4% of the value obtained by specific gravity determination.

The only previous report of pentamethylene chlorobromide is that of Magidson and Grigorowsky (6), who obtained it by the action of phosphorus tribromide and bromine on ω-benzoylaminoamyl chloride. Their product must have contained considerable quantities of the dibromide, for their density was 1.488, whereas the value obtained in the present investigation was 1.408. Also, the molecular refraction calculated from the values of the previous workers agrees rather poorly with the theoretical value.

Although the most obvious assumption is that the pentamethylene dibromide is formed by direct replacement of the chlorine by bromine (or, perhaps, *via* the hydroxy compound), it was thought possible that an intermediate is tetrahydropyran, for pentamethylene chlorohydrin has been reported (5) to lose halogen acid easily. This possibility was eliminated by treating trimethylene chlorohydrin with hydrobromic and sulfuric acids under similar conditions. This chlorohydrin gives a cyclic ether only on treatment with molten potassium hydroxide (6a); however, the halide obtained from the hydrobromic and sulfuric acid treatment contained considerable dibromide, and the rate of formation of dibromide was roughly parallel with that observed in the case of the pentamethylene derivative. Although some investigators (7) have treated trimethylene chlorohydrin with hydrobromic and sulfuric acids and assumed the product to be the chlorobromide, it seems safe to say that all products so obtained from chlorohydrins contain significant quantities of dibromide. It has already been pointed out by Cloke and co-workers (8) that trimethylene chlorobromide obtained by the hydrobromic acid method "contains considerable quantities of trimethylene dibromide". These workers obtained nearly quantitative yields of trimethylene chlorobromide by use of phosphorus tribromide on the chlorohydrin. No attempt has been made by us to apply this procedure for preparation of the pentamethylene chlorobromide, on account of the ease of cyclization of the pentamethylene chlorohydrin.

TABLE I

COMPOSITION OF PENTAMETHYLENE DIHALIDE MIXTURES

REFLUX TIME, HRS	YIELD, G.	SP. GR.$^{25}_{25}$	MOLE % $Br\text{-}(CH_2)_5\text{-}Cl$	% YIELD $Br\text{-}(CH_2)_5\text{-}Cl$
0.25	34.5	1.440	91	66
0.5		1.454	86	
1.0	39.2	1.465	81	65.5
2.0	41.1	1.474	78	66
5.0 (2.6 eq. of HBr)		1.545	54	

When the mixture of pentamethylene chlorobromide and dibromide was treated with an amount of potassium cyanide slightly in excess of the total bromide present in the mixture, there was obtained a 52% yield of a mixture of chloro- and bromo-capronitriles. Thus, this process makes possible a yield of halonitrile somewhat greater than that obtained from the dichloride. Obviously, alkylation of malonic ester with this mixture leads to a single product. By this route, the over-all yield of suberic acid from tetrahydropyran is about 30%.

By use of the specific gravity method, the composition of the halonitrile mixture was determined. It was found that the yield of bromonitrile, based on dibromide present in the halide mixture, was 52%, double the yield of bromonitrile obtained when pure pentamethylene dibromide is treated with the most favorable ratio of potassium cyanide. Furthermore, the yield of chloronitrile, based on chlorobromide used, is also 52%; therefore, considerable bromonitrile must have been obtained directly or indirectly from chlorobromide. This very likely results from replacement of chlorine in chlorobromide or chloronitrile by bromine from potassium bromide. This would actually be expected on account of the much lower solubility of potassium chloride in the reaction medium. Whatever may be the route, it follows that even if pure chlorobromide is used as starting material the product is a mixture of chloro- and bromo-nitriles, and bromonitrile formed before the potassium cyanide is exhausted would be readily converted to dinitrile, thus partially defeating the effectiveness of chlorobromide in increasing the yield of halonitrile. In view of the mixtures obtained and the labor of obtaining the starting materials, the use of polymethylene chlorobromides for making halonitriles seems hardly superior to the use of the dichlorides.

EXPERIMENTAL

Microanalysis by C. W. Koch and V. H. Tashinian. Boiling points are uncorrected. Reduced pressures were measured with a Zimmerli gage, unless otherwise specified. Specific gravities were determined in a bulb of about 3 ml. capacity and are accurate to about ±0.001 unit.

ω-Bromocapronitrile. Pentamethylene dibromide was prepared by the method of Wilson (9), using hydrobromic and sulfuric acids, in yields of 82–88%. A mixture of 230 g. (1 mole) of pentamethylene dibromide, 78 g. (1.2 mole[2]) of potassium cyanide, 160 ml. of water, and 650 ml. of 95% ethanol was heated under reflux for ten hours. The mixture was then distilled until about 550 ml. of distillate had been collected. After sufficient water had been added to the residue to dissolve precipitated salt, the oil phase was separated and the aqueous phase was extracted with three 35-ml. portions of benzene. After the oil and benzene extracts had been washed in sequence with 1 N sodium hydroxide they were combined and the solvent was flash-distilled. The residue was fractionally distilled through a 2-foot Vigreux column with heated jacket and total reflux head, collecting the products over ranges of about two degrees. Intermediate fractions were small (2–5 g.). The average yield of bromonitrile was 45 g. (26%), b.p. 133–135° (15 mm.). There was also obtained 27.5% yield of dinitrile and 17% recovery of dibromide. The bromonitrile fraction sometimes contained a trace of suspended white solid. This had no effect in the alkylation step. For the constant-boiling fraction of bromonitrile, b.p. 134.4° (15 mm.), n_D^{24} 1.4754, d^{24} 1.328, MR_D 37.41 (calc'd 37.35). Hauser and Breslow (10) reported b.p. 115–117° (6 mm.), for bromonitrile prepared from ω-bromocaproic acid.

ω-Chlorocapronitrile was prepared and isolated in the same manner as described for the bromonitrile except that four mole per cent of potassium iodide was added to the reaction mixture. In a 1.0-mole run, using 1.20 equivalent of potassium cyanide, the yield of chloronitrile was 49.3 g. (37.5%), b.p. 97–99° (5 mm.), and there was also obtained 24.8 g. (20%) of dinitrile, b.p. 141–144° (5 mm.). Recovery of dichloride was 26.5 g. (19%), b.p. 84–86° (26 mm.). For a constant-boiling fraction of chloronitrile, b.p. 121.0° (15 mm.), n_D^{23} 1.4488,

[2] Equivalencies of potassium cyanide in this paper are calculated on the basis of pure potassium cyanide, thus the values are a few per cent too high.

d^{25} 1.024, MR_D 34.51 (calc'd 34.46). This chloronitrile appears to have been reported previously only by Braun and Steindorff (11), who did not isolate it in a pure condition.

Pimelic acid. Pentamethylene dicyanide was prepared as described for the halonitriles, except that 2.1 equivalents of potassium cyanide were used and the product was distilled in a Claisen flask. Yields in several runs were 80–85%, b.p. 151–155° (3 mm.). For hydrolysis, 65 g. (0.53 mole) of the dinitrile was heated under reflux for three hours with 175 ml. of concentrated hydrochloric acid. The hot mixture was stirred vigorously in a beaker as it cooled, to prevent formation of an unworkable cake. After standing overnight, the semi-solid mass was pressed on a Büchner funnel, then stirred with 75 ml. of cold water. After collecting, washing with cold water, and drying there were obtained 91–94% yields of nearly white pimelic acid, m.p. 99–103°. This product is essentially pure but usually the melt is cloudy from traces of ammonium chloride, easily removed by recrystallization from water.

Diethyl ω-cyanoamylmalonate. To a solution of 5.7 g. (0.25 atom) of sodium in 200 ml. of absolute alcohol (distilled from sodium) was added 75 g. (0.47 mole) of diethyl malonate. After stirring this mixture for five minutes under reflux there was added during about five minutes 44 g. (0.25 mole) of ω-bromocapronitrile. This mixture was stirred under reflux until a test sample was no longer alkaline to phenolphthalein (1–2 hours). After most of the alcohol had been distilled from the mixture, with continued stirring to prevent bumping, the residue was shaken with water and benzene, and the aqueous phase was extracted again with benzene. The residue from the benzene extract was distilled in a Claisen flask at 2 mm. pressure. After a fore-run consisting largely of excess malonic ester, the cyanoester was collected at 155–165°, wt. 52.8 g. (81.5%, based on bromonitrile). Such material as this was used in the next step, but its homogeneity was checked by redistillation through a half-meter Podbielniak type column, measuring pressure with a McLeod gage. There was obtained 1.2 g. of fore-run, 49.0 g. of cyanoester of b.p. 161–162° (2 mm.), and 2.0 g. of distillation residue. For analysis, there was used a constant-boiling fraction of b.p. 161.9° (2 mm.), n_D^{22} 1.4425.

Anal. Calc'd for $C_{13}H_{21}NO_4$: C, 61.14; H, 8.29.
Found: C, 61.24, H, 7.95.

Alkylation with ω-chlorocapronitrile or the mixed halocapronitriles was carried out similarly and in essentially the same yields except that 25 mole per cent of potassium iodide was added to the reaction mixture, and alkylation was continued under reflux for about four hours. The composition of the mixed chloro- and bromo-capronitriles was determined by the density, and this value was used to determine the required equivalence of sodium.

Suberic acid. The cyanoester was hydrolyzed by heating under reflux with stirring for 3–4 hours with 7 *N* aqueous hydrochloric acid (5 ml. per g. of cyanoester). On cooling this mixture, 1,1,6-tricarboxyhexane crystallizes, but it is most convenient not to isolate this rather soluble intermediate. Water and acid were distilled from the reaction mixture and the residue was heated at 180–190° until carbon dioxide evolution had ceased (usually 60–90 minutes). The residue of suberic acid and ammonium chloride was heated with water under reflux with stirring for a few minutes, using 100 ml. of water per 0.2 mole of starting cyanoester. Suberic acid was filtered from the cooled solution and washed with cold water. The yield of slightly gray acid amounts to 90–95% of the theoretical amount, m.p. 138–141°. The melt is usually cloudy from ammonium chloride, which may be removed, if desired, by crystallization from a mixture of benzene and alcohol. Once-recrystallized acid melted at 139–141°.

ω-Acetoxyamyl chloride was prepared by a modification of the method of Synerholm (5). A mixture of 175 g. (2.03 moles) of tetrahydropyran, dried over sodium hydroxide, 8 g. of freshly-fused zinc chloride, and 159 g. (2.03 moles) of acetyl chloride, distilled from dimethylaniline, was heated under reflux for two hours. The cooled reaction mixture was filtered and directly distilled from a Claisen flask. After a fore-run of low-boiling material, the chloroester was collected at 109–112° (24 mm.), weight 294 g. (88%). From the literature (5), b.p. 104° (18 mm.) or 113–115° (34 mm.).

Mixed pentamethylene halides. A mixture of 56.6 ml. (0.5 mole) of 48% hydrobromic acid,

41.2 g. (0.25 mole) of ω-acetoxyamyl chloride, and 28 ml. (0.5 mole) of 96% sulfuric acid was heated under reflux for varying lengths of time. The crude product was washed with three 20-ml. portions of concentrated sulfuric acid, then with water, bicarbonate solution, and water, and finally dried over calcium chloride. On distillation at reduced pressure, the product was collected in the range 90–105° (15 mm.). Yields and compositions of the products are found in Table I. In a 1.8-mole run heated for two hours the yield of mixed halides was 87% of the theoretical number of moles, and the mixture contained 77 mole per cent of pentamethylene chlorobromide.

Data for analysis of pentamethylene dihalide mixtures. Pentamethylene dibromide, prepared by the method of Wilson (9) was washed repeatedly with sulfuric acid, and further purified as described for the mixed halides. On distillation, the total product was collected at 98–99° (15 mm.). The sp. gr.$^{25}_{25}$ for fractions taken near the beginning and end of the distillation were respectively 1.703 and 1.705. The value 1.704 was used for calculation of compositions of mixtures.

In order to obtain a sample of pure pentamethylene chlorobromide, a sample of mixed halides, sp. gr.$^{25}_{25}$ 1.471 was distilled through a 1-meter column packed with glass helices, at a pressure of 30 mm. Fractionation data are given in Table II. Fraction 2 was collected in six sub-fractions, and the sp. gr.$^{25}_{25}$ for the second, third, and fifth of these were determined, respectively, as 1.407, 1.408, 1.408. The latter value was used for calculating compositions. The value for n^{25}_{D} for Fraction 2 was 1.4838, thus MR_D was 37.71 (calc'd 37.92).

TABLE II

FRACTIONATION OF MIXED PENTAMETHYLENE DIHALIDES

FRACTION NO.	COMPONENTS	B. P. °C (30 MM.)	WT., G.
1	Dichloride and chlorobromide	90.5–102.4	3.6
2	Chlorobromide	102.4	82.1
3	Chlorobromide	102.4–103.2	8.0
4	Chlorobromide and dibromide	103.2–118.5	6.8
5	Dibromide	118.5–119	35.6

From the specific gravity of the mixture distilled, 1.471, its composition is calculated as 78.6 mole per cent pentamethylene chlorobromide. From the data in Table II, the chlorobromide content of the mixture is calculated as 74.4 mole per cent, if it is assumed that Fraction 1 is one third dichloride and two thirds chlorobromide, and Fraction 4 is equal amounts of chlorobromide and dibromide. This would seem adequate proof that no impurities in the reaction mixtures are rendering invalid the analyses based on specific gravity.

The validity of linear extrapolation between the respective specific gravities of the dibromide and chlorobromide was established by determination of the gravities of mixtures prepared from weighed amounts of the two pure components. The known dibromide contents of the mixtures, followed in parentheses by the values calculated from specific gravity determinations, were: 75.2% (75.0%), 56.4% (57.1%), 35.1% (35.8%). Thus, within the limits of our experimental accuracy, the two dihalides form a perfect solution over the entire range of composition.

Mixed trimethylene dihalides were prepared from a sample of commercial trimethylene chlorohydrin, using the same procedure as described for the pentamethylene dihalides. The products obtained from runs which had been heated under reflux for one quarter hour and two hours, respectively, were found to have sp. gr.$^{25}_{25}$ of 1.673 and 1.717. Using literature values for densities of trimethylene dibromide, d^{15} 1.987, and the chlorobromide[3], d^{8} 1.63,

[3] Although trimethylene chlorobromide has been prepared by numerous investigators. the chief analytical interest has been analysis of mixtures of the 1,2- and 1,3-chloro-

approximate values for the chlorobromide content of these mixtures were calculated; after fifteen-minute reflux, 88%; after two-hour reflux, 74%. By reference to Table I, it may be seen that these values are in rather good agreement with the values obtained in the pentamethylene dihalide series.

Mixed ω-bromo- and ω-chloro-capronitriles were prepared by the procedure described for ω-bromocapronitrile, using 44.3 g. (0.68 mole) of potassium cyanide and 0.5 mole of mixed pentamethylene dihalides (97.9 g. of sp. gr.$^{25}_{25}$ 1.477; 0.385 mole of chlorobromide and 0.115 mole of dibromide). Fractionation of the product through the 2-foot Vigreux column at 2 mm. pressure gave the following: (a) fore-run, b.p. 46–88°, wt. 5.5 g.; (b) mixed halonitriles, b.p. 88–107°, wt. 37 g.; (c) intermediate, b.p. 107–134°, wt. 3.4 g.; (d) dinitrile, b.p. 134–135°, wt. 14.0 g. For the halonitrile fraction, sp. gr.$^{25}_{25}$ 1.094. From the specific gravities of the pure halonitriles, as reported under their preparation, the halonitrile mixture is calculated to be 23 mole per cent bromonitrile. Thus, the yield of chloronitrile is 0.202 mole (52% based on chlorobromide used), and the yield of bromonitrile is 0.0595 mole (52%, based on dibromide used). Thus, the conversion of chloronitrile to bromonitrile by reaction with potassium bromide is clearly indicated, unless it be assumed that reaction of chlorobromide with potassium cyanide can yield appreciable quantities of bromonitrile.

The validity of analysis of the halonitrile mixture by use of density depends on the absence of other products of different density, such as dibromide or dinitrile. Such materials were shown to be almost entirely absent by fractionation of the products of two runs through a 3-foot packed column at 15 mm. pressure. Fractions obtained were: (a) fore-run, b.p. 114–121°, wt. 1.5 g.; (b) chloronitrile, b.p. 121–122°, wt. 40.6 g.; (c) intermediate, b.p. 122–134°, wt. 3 4 g.; (d) bromonitrile, b.p. 134–134.5°, wt. 21.6 g.; (e) residue, less than 1 g.

In one of the runs used for fractionation, only 35.8 g. of potassium cyanide was used, but this was found to be inconvenient for synthesis of halonitriles, for some pentamethylene dibromide was recovered, and this is separated from the chloronitrile only by careful fractionation.

SUMMARY

There is described a convenient synthesis of suberic acid depending on alkylation of malonic ester with an ω-halocapronitrile, followed by hydrolysis and decarboxylation.

ω-Bromo- and ω-chloro-capronitriles were prepared by reaction of the appropriate pentamethylene dihalide with 1.2 equivalent of potassium cyanide.

Pentamethylene chlorobromide was prepared by reaction of hydrobromic acid with ω-acetoxyamyl chloride, but there was always obtained a considerable amount of pentamethylene dibromide. Pure polymethylene chlorobromides may be obtained by this method only if dibromide is separated by fractional distillation.

It is shown that reaction of pentamethylene chlorobromide with potassium cyanide yields ω-chlorocapronitrile admixed with ω-bromocapronitrile.

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bromides, and the only available value for the density of the 1,3-chlorobromide is that reported in early work by Reboul (12), but this value appears of about the expected magnitude. The value (sp. gr.$^{20}_{20}$ 1.4718) reported by Rossander and Marvel (13) is obviously in large error, as is evident from comparison with values for the dibromide (1.99) and the dichloride (1.20). The same workers reported a very low value for the dichloride.

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[Contribution from the Laboratory of Organic Chemistry of the University of Wisconsin]

THE SYNTHESIS OF HEXESTROL THROUGH THE CATALYZED-GRIGNARD COUPLING OF ANETHOLE HYDROBROMIDE AND THE MECHANISM OF THE REACTION

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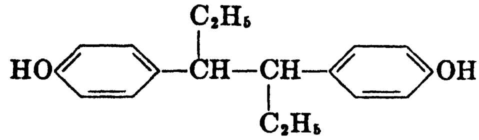
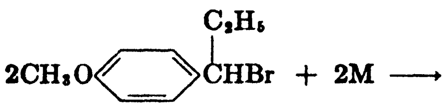
The first practical synthesis of the estrogen hexestrol (I),

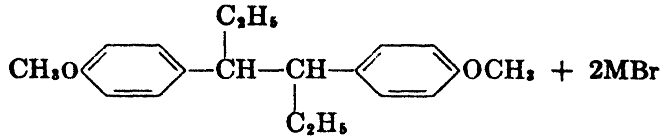


I

discovered by Dodds, *et al.* (1), was reported in 1940 by Docken and Spielman (2) and independently by Peak and Short (3) and Bernstein and Wallis (4). This synthesis involved a Wurtz-type coupling of anethole hydrobromide (II) to hexestrol dimethyl ether (III):



II



III

The yield of the *meso* isomer of hexestrol dimethyl ether by this reaction was 15 to 20% using metals such as magnesium and sodium, and somewhat lower (6%) employing a Grignard reagent such as methylmagnesium iodide (5). In 1943 Kharasch and Kleiman (6) described an improved Grignard coupling procedure using phenylmagnesium bromide in the presence of catalytic amounts of cobaltous chloride, and reported yields as high as 42% of the *meso* ether III.

The coupling of benzyl halides to dibenzyls by the action of Grignard reagents in the presence of a catalyst (or "uncatalyzed") has been studied by many investigators, notably Spaeth (7), Job (8), Fuson (9) and more recently Vavon (10). The outstanding contribution of Kharasch and his co-workers (11) to this and related reactions of Grignard reagents has been to point out the effectiveness of cobaltous chloride in catalytic amounts and to investigate more fully the nature and scope of the reactions.

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We have been interested in studying the catalyzed-Grignard synthesis of hexestrol in some detail and have investigated the effect of the Grignard reagent and a number of other factors on the yield of III. We have been unable to arrive at the yield reported by Kharasch and Kleiman with phenylmagnesium bromide, but have developed what we believe to be a more practical procedure using ethylmagnesium bromide, which has given consistent yields of 31–34% of the *meso* dimethyl ether III. Our experiments also have illuminated certain aspects of the mechanism of th's reaction.

In a series of runs under similar conditions, employing anethole hydrobromide and different Grignard reagents in the presence of five to seven mole per cent of cobaltous chloride, the highest yields (29–31%) of the *meso* ether III were obtained with the ethyl Grignard reagent, while with the phenyl, methyl, isopropyl, or *tert*-butyl reagents the yields were significantly lower (23–25%). The coupling reaction was poorer with anethole hydrochloride, giving 19–23% yields of III with ethyl-, isopropyl-, *tert*-butyl- or phenyl-magnesium bromide and only 12% with methylmagnesium bromide. Anethole hydriodide was not suitable for the reaction (2% yield) apparently due to polymerization of the anethole during addition of hydrogen iodide. In the hydrobromide series, then, the best yield obtained (31%) was considerably below the highest reported by Kharasch and Kleiman (42%) when five mole per cent of cobaltous chloride was used, but was comparable to their yields (27%) using fifteen mole per cent of catalyst.[2]

Next the effect of temperature was investigated. Since anethole hydrobromide and ethylmagnesium bromide proved to be the best combination, most of the subsequent work was carried out with these. Variations over the range −20° to 30° had a negligible effect on the yield of III; the yield was slightly higher at the higher temperatures. With phenylmagnesium bromide, however, there was a definite rise in yield with temperature reaching a maximum of 32% at 20°. At 30° the yield was considerably lower (17%). These results, particularly with the ethyl derivative, are in contrast with the statement of Kharasch and co-workers (11, 12) that a rise in temperature caused deterioration and deactivation of the catalyst.[3]

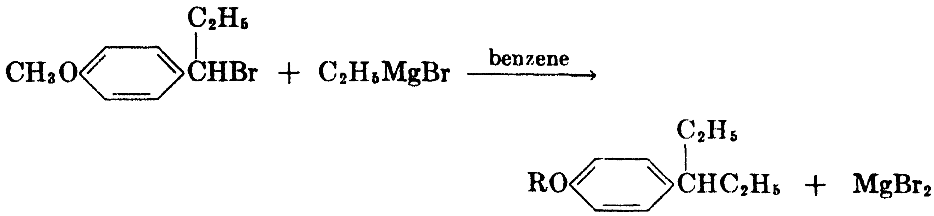
The use of a larger excess of Grignard reagent or more cobaltous chloride (five to fifty mole per cent with a constant excess of Grignard reagent) had no appreciable effect on the yield, nor did varying the time for addition of anethole hydrobromide from five to one hundred and ten minutes. The reaction, as judged by the evolution of gas, appeared to be complete in each case within one-half minute after the end of addition. The same yields were obtained whether ordinary commercial magnesium turnings were used to prepare the Grignard

[2] In this connection it should be mentioned that, in our hands, this variation in the amount of catalyst did not affect the yield, nor did further addition of small amounts of catalyst after part of the anethole hydrobromide had been added.

[3] It would appear that Kharasch may have modified his views on this point, since recently (13) some cobaltous chloride-catalyzed reactions have been carried out at 100°, and indeed with better results than at lower temperatures. To be sure, these reactions were attributed to breakdown of the organo-cobalt intermediate to form radicals—perhaps a different mechanism from that operating here. See, however, footnote 7.

reagent or a very pure sample of sublimed magnesium; filtering the Grignard solution also failed to improve the yield. These results would appear to eliminate impurities in the magnesium as the explanation of the discrepancy between our yields and that of Kharasch and Kleiman.

In all of these runs ether was employed as the solvent. When this was replaced by benzene, none of the desired methyl ether III could be isolated and instead the major product was that of alkylation (IVa). In



IVa, R = CH_3
(IVb, R = H)

di-*n*-butyl ether the yield of the *meso* ether III was only 5%. It seems possible that the ineffectiveness of the cobaltous chloride catalyst in benzene may be due to insolubility.

Thus, the most satisfactory procedure for preparing hexestrol dimethyl ether was found to be the coupling of anethole hydrobromide in the presence of ethylmagnesium bromide and cobaltous chloride.[4] Consistent yields of 31–34% of the *meso* isomer could be obtained over a fairly wide range of reaction conditions. Ethylmagnesium bromide was superior to phenylmagnesium bromide because of greater ease in isolating the product. With the phenyl reagent, a large amount of biphenyl is formed which interferes with crystallization of the product unless removed by steam distillation; with ethylmagnesium bromide the corresponding by-products are gases.

In order to gain further insight into the reaction the material remaining after crystallization of the *meso* ether III was fractionally distilled, giving two main fractions, b.p. 95–110° (8–12 mm.) and b.p. 160–180° (0.1–0.3 mm.). From the latter the racemic dimethyl ether (2) corresponding to III could be crystallized; the yield of this isomer was slightly less than that of the *meso* isomer, amounting to 25–30% for the runs using ethylmagnesium bromide and anethole hydrobromide (11–14% using anethole hydrochloride). The remainder of this fraction (5–8%), an oil which did not crystallize, probably contained some of the dimer isoanethole.

The lower-boiling fraction amounted to about 15% of the weight of the anethole used in the hydrobromide runs and 30% in the hydrochloride runs. By titration with bromine in carbon tetrachloride these fractions were found to

[4] It was of interest to see if cobaltous chloride would increase the yield of the dimethyl ether III when the procedure of Docken and Spielman (2) was used, employing magnesium instead of a Grignard reagent. In the presence of seven mole per cent of cobaltous chloride the yields were increased from 15–20% to around 25%. This may indicate the formation of a Grignard reagent as an intermediate in this reaction (*cf*. Ref. 14).

contain about 27% and 10%, respectively, of unsaturated material, presumably anethole. Initially it was assumed that the saturated component of this fraction was the product of alkylation of the anethole hydrohalide with the ethyl Grignard reagent, and this was indeed the case with anethole hydrochloride. After demethylation, crystalline 3-(*p*-hydroxyphenyl)pentane (IVb) was isolated and identified by comparison with a synthetic sample. In the case of anethole hydrobromide, however, only a small amount of the alkylation product IVa was formed, and the main saturated component of this fraction was *p*-*n*-propylanisole; this was identified as the crystalline 3,5-dinitrobenzoate of *p*-*n*-propylphenol after demethylation and esterification. When the cobaltous chloride was omitted, the alkylation product was the major product, even with anethole hydrobromide; this constitutes a simple method of preparing 3-(*p*-anisyl)pentane (IVa) in 82% yield.[5]

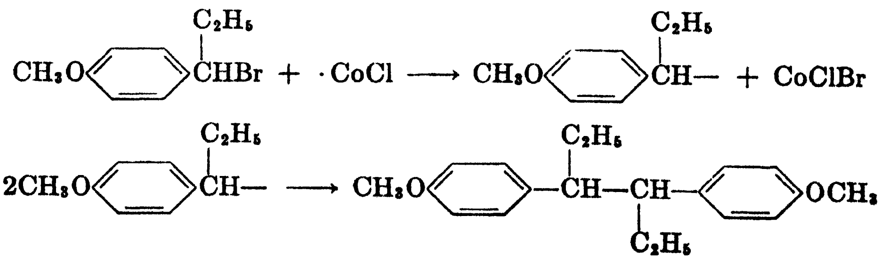
The major factor responsible for the variations in yield of *meso*-hexestrol dimethyl ether (III) resulting from changes in the anethole hydrohalide (chloride or bromide) or in the Grignard reagent, seems to be the effect on the relative rates of the catalytic reaction and the alkylation reaction, for when the yield of III was lowered the amount of alkylation product (in Fraction 1) was increased. In the runs using anethole hydrochloride and ethylmagnesium bromide, the amount of this alkylation could be diminished, with an accompanying increase in the yield of III from 22 to 26% (a small but significant difference), by adding the Grignard reagent along with the anethole hydrochloride. Corresponding runs with anethole hydrobromide, however, resulted in no improvement, (indeed the yield was lower), in agreement with the finding that relatively little alkylation occurred with these reagents in the normal procedure.

MECHANISM OF THE REACTION

Kharasch and his co-workers (6, 11, 12, 15) have investigated a great many reactions with Grignard reagents in the presence of catalytic amounts of cobaltous chloride. The mechanism which they have proposed is as follows, applied to the coupling reaction of anethole hydrobromide in the presence of phenylmagnesium bromide:

$$C_6H_5MgBr + CoCl_2 \longrightarrow C_6H_5CoCl + MgBrCl \qquad (A)$$

$$2C_6H_5CoCl \longrightarrow C_6H_5C_6H_5 + 2\cdot CoCl \qquad (B)$$



(C)

(D)

[5] The failure to obtain any of III was unexpected in view of the findings of Fuson (9) that benzyl halides are coupled to dibenzyls by Grignard reagents (also Ref. 5).

The reaction is believed to be a chain reaction involving free radicals with cobaltous subhalide postulated as the chain propagator.

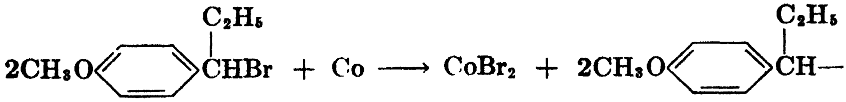
Several features of this mechanism seem to us to be inconsistent with the reaction as we have observed it. In the first place, all attempts to prepare organo-cobalt compounds as postulated in equation A have indicated these to be unstable compounds (16, 17, 18) decomposing at once to metallic cobalt and the coupling or disproportionation products of the organic group.[6] Secondly, there is no experimental evidence to indicate the stable existence of the cobaltous subhalide proposed as the reactive intermediate in equation B. To be sure, each of these might be postulated as possible intermediates in the reaction, but it seems certain that they would be very short-lived. Yet our observations indicate that the reaction of the Grignard reagent with cobaltous chloride can be carried out several hours before the addition of the anethole hydrobromide. Indeed some catalytic activity was retained by the Grignard-cobaltous chloride mixture after standing at room temperature for several days or even weeks. This seems incompatible with the above mechanism, since equations A and B should proceed in the absence of the anethole hydrobromide, and the reactive intermediates would decompose to give metallic cobalt. In addition, the organic product formed in reaction B presents a dilemma, for if the phenylcobaltous chloride intermediate decomposed to give the radical $\cdot CoCl$, it might be expected that the other product would be the phenyl radical. Yet, as pointed out by Kharasch and co-workers (11), phenyl radicals generated in solution by other methods do not combine to give biphenyl as in this reaction, but instead give a variety of products (by disproportionation, attack on the solvent, etc.). To avoid this dilemma, the breakdown in equation (B) must be considered to occur in some other manner, as yet obscure, not involving phenyl radicals.[7]

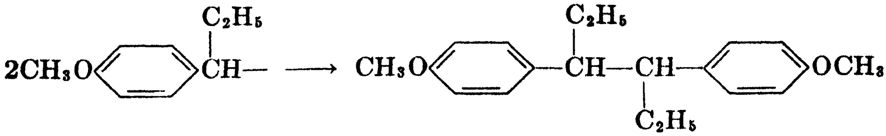
These facts and others which will be presented below can be reconciled, however, with a chain mechanism in which cobalt metal is the reactive intermediate. The cobalt formed by decomposition of the unstable organo-cobalt compound is in a very finely divided and reactive form and may be considered to effect a Wurtz-type of reaction with the anethole hydrobromide, very likely with the intermediate formation of the free radical from the halide:

$$2C_2H_5MgBr + CoCl_2 \longrightarrow MgBr_2 + MgCl_2 + [(C_2H_5)_2Co] \longrightarrow C_2H_6 + C_2H_4 + Co \quad (E)$$

[6] However, starting with organozinc compounds Job and Reich (19) believed they obtained organo-cobalt derivatives.

[7] Recently Kharasch and Urry (13) have concluded that a similar breakdown with aliphatic Grignard reagents and cobaltous chloride does give rise to free alkyl radicals as intermediates. It seems to us, however, that the experimental evidence upon which this is based is still inconclusive, since radicals are believed to be formed from the alkyl halide also present; thus, reactions indicating their presence cannot be attributed to organometallic breakdown in the absence of additional evidence. Indeed the different proportion of products resulting from such "radicals" from the organo-metallic intermediates, compared with those generated from diacyl peroxides, suggests that they are too short-lived to be considered true radicals in solution. A definitive test for their existence would appear to be a reaction similar to those described by Kharasch and Urry but *in the absence* of alkyl halide and with a full equivalent of cobaltous chloride to carry the reaction to completion.

 (F)

 (G)

According to this mechanism the catalytic activity of the Grignard-cobaltous chloride mixture would be retained indefinitely, or as long as the cobalt metal remained in its active, finely divided form. Kharasch and Fields (11) observed differences in the stability of the catalyst prepared from aryl and alkyl Grignard reagents. They reported that a solution of phenylmagnesium bromide and cobaltous chloride retained about 50% of its catalytic activity after refluxing in ether solution for one and one-half hours, while the catalyst from methylmagnesium bromide was practically completely destroyed under these conditions. Their explanation of these results on the basis of varying stabilities of the aryl- and alkyl-cobalt intermediates hardly seems tenable, since neither type of organo-cobalt compound would be expected to survive such conditions. The results are explainable on the basis of the metallic cobalt mechanism, since Job and Reich (19) and Dupont and Piganiol (17) have reported that the colloidal cobalt prepared using an alkyl Grignard reagent is more easily flocculated than that from a phenyl Grignard reagent, which seems to stabilize the colloidal solution. With coagulation of the colloidal solution the reactivity of the cobalt was lost. In our own experiments we have found that the catalytic activity of the cobalt is not lost when the reaction is carried out at temperatures as high as 35°, provided an excess of Grignard reagent is present; this is doubtless due to the fact that the finely divided cobalt is continually regenerated in a chain reaction, thus preventing flocculation.

The products observed from the Grignard reagent in the cobaltous chloride-catalyzed reactions are those to be expected from decomposition of an unstable organo-metallic compound, *viz*, a diaryl from an aryl Grignard reagent (11), disproportionation products from higher alkyl Grignard reagents, (*e.g.* butene and butane from *n*-butylmagnesium bromide) (20), and principally methane from the methyl Grignard (13, 20), although the available evidence for alkyl organometallic compounds is scanty.

The reaction of finely divided cobalt metal with anethole hydrobromide (equations F and G) is analogous to the earlier procedures (2, 3, 4) where magnesium or sodium was used. It may be considered to lie at one extreme of reactions of the Wurtz type since the cobalt probably only removes the halogen to give a free radical and does not react further to give an organo-metallic intermediate at this stage. Kharasch and his co-workers have pointed out that the products obtained in this type of reaction are indicative of free radicals rather than unstable organo-metallic compounds, since dimers are formed only with a few special halides which would form the more stable radicals, while most of the others, including aryl halides, give disproportionation products.

In order to provide experimental confirmation for reactions F and G, runs were carried out in which the Grignard reagent was used up by reaction with an equivalent amount of cobaltous chloride. The resulting suspension of cobalt metal, which now could not be regenerated during the reaction, was found to give 8.5% of *meso*-hexestrol dimethyl ether when treated with anethole hydrobromide. Although this yield is lower than that obtained in the usual procedure, it can be attributed to a less favorable state of subdivision of the cobalt metal than when it is continually regenerated in the chain reaction. In support of this view, the yield of III was increased to 15% when the cobalt was first "recycled" to increase the state of subdivision of the metal by allowing it to react with an equivalent mixture of ethyl bromide and ethylmagnesium bromide *prior* to the addition of the anethole hydrobromide.[8]

The course of the reaction of anethole *dibromide* with ethylmagnesium bromide in the presence of catalytic amounts of cobaltous chloride might be considered to support the proposed new mechanism. If cobaltous subchloride were the reactive intermediate it might be expected to give to an appreciable extent a free radical similar to that postulated in equation (C) or (F), but containing a bromine atom, resulting in a significant amount of coupling to dimeric or polymeric products. If cobalt metal were the reactive intermediate, on the other hand, it would not be unexpected for simple debromination to occur, giving anethole. Actually anethole was obtained in this reaction in 92% yield.

It seems probable that the low-boiling by-products of the coupling reaction, anethole and *p*-*n*-propylanisole, result from some intermediate involved in the coupling reaction itself, rather than from an independent reaction, for the total amount of these by-products was remarkably constant throughout the variations in conditions, although there was considerable change in their ratio. They might be considered as arising from the free radical intermediate in equation (F), either by disproportionation or attack on the solvent.

This mechanism involving cobalt metal can be used satisfactorily to explain most of the other Grignard reactions catalyzed by cobaltous chloride, including the dimeric reduction of certain ketones to pinacols and related reactions (22).

EXPERIMENTAL[9]

Anethole hydrobromide. Through a solution of 100 g. of anethole (Eastman Kodak Co.)[10] in 400 cc. of 40–60° petroleum ether cooled in an ice–salt bath was passed dry hydrogen

[8] It is difficult to rule out completely the cobaltous subchloride postulate, and we recognize that it is possible that after the cobalt metal has initiated the reaction, cobaltous subchloride might exist as a short-lived intermediate which could help continue the chain reaction. Indeed some of the products obtained with cobaltous chloride-catalyzed Grignard reagents are similar to those produced by the binary magnesium-magnesium iodide mixture of Gomberg and Bachmann (21), for which magnesious iodide has been suggested as the reactive component. Docken (5) has found that this binary mixture gives III in 11% yield. However, for the present reaction there is no direct evidence to support the cobaltous subhalide hypothesis or need for its postulation, since the concept of finely divided, reactive cobalt metal seems to be in good accord with the observed facts.

[9] All melting points are corrected.

[10] Redistillation of the anethole just prior to use had no appreciable effect upon the yields.

bromide gas at such a rate that the temperature remained below 0°. Near the end of the reaction the temperature fell to −20°; completeness of addition was ascertained by testing for unsaturation with a 5% solution of bromine in carbon tetrachloride. The petroleum ether was then removed under water pump pressure, employing a capillary tube attached to a calcium chloride tube to allow dry air to sweep through the liquid. The temperature fell to about −40° until most of the solvent was removed, and then rose to about −10°. The oily anethole hydrobromide was dissolved in anhydrous ether and used immediately.

Similarly anethole hydrochloride was prepared using dry hydrogen chloride, and anethole hydriodide with dry hydrogen iodide. In the latter case a considerable amount of viscous tar was formed, due to polymerization.

Cobaltous chloride. For most of the runs anhydrous cobaltous chloride was prepared by drying the hexahydrate in the oven, finally at 190° for about ten hours, then it was finely powdered and dried for several hours longer. The material gave a clear solution in water. The same results were obtained with this catalyst as with that prepared by the method of Kharasch (11) involving heating in a stream of dry hydrogen chloride.

Hexestrol dimethyl ether (best procedure—Run 22, Table I). Ethylmagnesium bromide was prepared in a 3-l., four-necked flask fitted with a reflux condenser, mercury-sealed Hershberg stirrer, dropping-funnel and thermometer, using 29 g., (1.19 mole) of magnesium turnings, 129 g. (1.17 mole) of ethyl bromide, and 1000 cc. of dry ether. The yield of Grignard reagent was 85%. Meanwhile anethole hydrobromide was prepared as described above from 100 g. (0.68 mole) of anethole.

To the stirred Grignard solution at room temperature was added 6.75 g. (0.052 mole) of anhydrous cobaltous chloride over a one-minute period. The system was then attached to a mineral oil trap and a solution of the anethole hydrobromide in 225 ml. of dry ether was added over a period of thirty minutes, with the temperature at 30–31°. The vigorous evolution of gas stopped within one-half minute after addition was complete and the temperature began to fall. (Tests in other runs showed the reaction to be complete at this point.)

The black mixture was poured onto ice and hydrochloric acid and extracted twice with ether, the extracts being thoroughly washed with 5% hydrochloric acid, water, saturated salt solution and dried over calcium chloride.[11] After removing the ether the residual yellow oil was dissolved in 250 cc. of methanol and allowed to crystallize in the refrigerator; 30.9 g. (31%) of *meso*-hexestrol dimethyl ether was obtained, m.p. 140–143°.[12]

The filtrate was concentrated and distilled under reduced pressure giving a first fraction of 14.5 g., b.p. 105–120° (12 mm.), n_D^{25} 1.5158, a second fraction of 38.2 g., b.p. 175–195° (0.6 mm.) and a third fraction of 7.8 g., b.p. 240–290° (1–2 mm.) with decomposition. The second fraction was dissolved in 100 cc. of methanol and allowed to stand for several days in the refrigerator, resulting in 27.4 g. (27%) of racemic hexestrol dimethyl ether, m.p. 53–56°. In some runs a small first crop of the *meso* isomer was obtained here.

meso-Hexestrol. A mixture of 30 g. of *meso*-hexestrol dimethyl ether (m.p. 143.5–144°), 500 cc. of acetic acid, and 200 cc. of 48% hydrobromic acid was refluxed for ten hours and then poured into 3 liters of water. After cooling, the solid was filtered, washed, and dried at 85°, giving 26.1 g. (96%) of hexestrol, m.p. 181–185°. Recrystallization from benzene gave 73% recovery of pure *meso*-hexestrol (dried at 80°) in the first crop, m.p. 186–187°, and an additional 23%, m.p. 182.5–185.5°.

Variations in the coupling reaction. In Table I are summarized runs in which various reagents or conditions were changed in the coupling reaction. When phenylmagnesium bromide was used, the reaction mixture was either steam distilled to remove biphenyl or the *meso* ether carefully crystallized from methanol and the biphenyl removed from the filtrate by distillation (around 90–140° at 8 mm.). The product of alkylation by the phenylmagnesium bromide appeared in Fraction 2 (b.p. 140–185° at 0.3 mm.) along with the racemic ether and anethole dimers. It could not be obtained crystalline.

Variation in the method of addition. A run was made in which 0.1 mole of ethylmagnesium

[11] With sodium sulfate some of the product was removed by adsorption.

bromide solution was added at 30° simultaneously with 0.1 mole of anethole hydrochloride solution to a stirred suspension of the catalyst prepared by reducing 1 g. (0.0077 mole) of cobaltous chloride in 50 cc. of ether with 0.01 equivalent of the Grignard solution. The yield of *meso* ether was increased to 26% (m.p. 140–142°), that of racemic ether to 22% (m.p. 53–56°) and the amount of Fraction 1 was reduced to 2.1 g. However, this method of addition was not beneficial with anethole hydrobromide, the yield of *meso* ether being 22% and of racemic ether 16%.

Runs using equivalent amounts of cobaltous chloride and Grignard reagent. To an ether solution of 0.11 equivalent of ethylmagnesium bromide was added 15 g. (0.115 mole) of cobaltous chloride over a period of four minutes at 10°. After the addition, titration indicated the presence of 0.009 equivalent of basic material (which probably was due to the finely divided cobalt rather than Grignard reagent). A solution of 0.1 mole of anethole hydrobromide was added during ten minutes at 15–20°. After stirring for one hour the mixture was worked up as before to give a total of 1.28 g. (8.6%) of the *meso* ether (mainly 139–142° in m.p.). The yield was the same when cobaltous bromide was used.

When the cobaltous chloride (0.055 mole) was reduced by adding a mixture of 0 15 equivalent of ethylmagnesium bromide and 0.16 mole of ethyl bromide over a period of twenty minutes and "recycled" by addition of another 0.15 equivalent of Grignard reagent and 0.03 mole of ethyl bromide (titration showed presence of only 0.009 equivalent of basic material at this point) before adding the anethole hydrobromide (0.1 mole), the yield of *meso* ether was increased to 15%.

Retention of catalyst activity on standing. The yield was unaffected (32%) in a run by the usual procedure, when the Grignard-cobaltous chloride mixture was allowed to stand at room temperature for four hours before adding the anethole hydrobromide. Qualitative experiments to test for retention of catalytic activity were also made using ethylmagnesium bromide (0.15 equivalent) and 0.0077 mole of cobaltous chloride, followed by addition of 0.01 mole of ethyl bromide to give some "recycling." The activity was checked periodically by treating an aliquot with 0.01 mole of ethyl bromide and determining the amount of gas evolved. The catalytic activity decreased slowly over the first two days as the cobalt became less finely divided and settled out of suspension; considerable activity was left after nine days and some even after standing for sixteen days at room temperature.

Runs using magnesium (Docken–Spielman procedure). To a mixture of 5 g. (0.21 mole) of magnesium, 200 cc. of ether, and a few crystals of iodine was added 1 g. of cobaltous chloride and the solution cooled in an ice-salt bath to −10°. A small amount of the ether solution of anethole hydrobromide was added, and as there was no apparent reaction, 1 ml. of ethyl bromide was added and the temperature raised to 8° until some erosion of the magnesium was observed, then the remainder of the anethole hydrobromide (0.1 mole) was added at −10° over a forty-minute period. The mixture was stirred for one and one-half hours at 0°, three hours at 10–15°, four hours at room temperature and one hour at reflux, then worked up as before. The total yield of *meso*-hexestrol dimethyl ether was 25% (m.p. 140.5–142°) with 24% of the racemic ether. In another run using 0.25 g. of cobaltous chloride and no ethyl bromide, starting the addition at 0°, then continuing at −5° after the reaction began, the yield of meso ether was 22% with 20% of racemic ether.[13]

Investigation of Fraction 1. The low-boiling fraction from ethylmagnesium bromide runs with anethole hydrochloride was demethylated by heating 5.06 g. (b.p. 95–110° at 10 mm., n_D^{25} 1.5089, containing an estimated 11% of anethole) with 125 cc. of acetic acid and 25 cc. of 48% hydrobromic acid for eleven hours. After dilution and extraction with ether the phenol was distilled, giving 1.9 g. of clear liquid, b.p. 122–125° (12 mm.) which solidified. After several recrystallizations from petroleum ether (40–60°) the m.p. of the solid was 75.5–76°, and was not depressed when mixed with a synthetic sample of 3-(*p*-hydroxyphenyl)pentane, m.p. 76.5–77°.

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[13] With larger runs (330 g. of anethole) for which the amount of solvent was proportionately about one-half that described here, the yields of the *meso* ether dropped to 19.5–23.5%.

TABLE I
CONDITIONS AND YIELDS OF PRODUCTS

RUN NO.	ANETHOLE Moles Used	ANETHOLE Halide Used	GRIGNARD REAGENT Halide Used	GRIGNARD REAGENT Moles of Reagent[a]	MOLE % $CoCl_2$	TEMP., °C	TIME OF ADDN. MINS.	MESO ETHER[r] %	RACEMIC ETHER[s] %	FRACTION 1 g.	FRACTION 1 n_D^{25}	FRACTION 1 % anethole[b]	TOTAL WEIGHT FRACTION 2 G.	RESIDUE G.
1	.34	Cl	CH_3Br	(0.70)	4.5	0–5[c]	150	12	7	23.8	1.5374	44	10.5	5.5
2	.34	Cl	C_2H_5Br	(0.70)	4.5	0–5[c]	25	22	11	15.0	1.5070	11	15.4	4.8
3	.34	Cl	C_2H_5Br	(0.70)	4.5	−5–0	20	21	14	16.2	1.5095		15.3	4.8
4	.34	Cl	i-C_2H_7Br	(0.70)	4.5	−5–0	55	23	15	15.1	1.5110	14	16.3	4.3
5	.34	Cl	t-C_4H_9Cl	(0.70)	4.5	−5–0	50	15	6	19.2	1.5065	4	10.8	6.4
6	.34	Cl	t-C_4H_9Br	(0.70)	4.5	−5–0	80	21	9	16.3	1.5053		14.2	4.8
7	.34	Cl	C_6H_5Br	(0.70)	4.5	−5–0	55	19	7	[d]			21.1[d]	8.8
8	.10	Br	CH_3Br[e]	0.17	7.7	0	15	25	20	3.1	1.5420	72	5.4	0.85
9	.34	Br	C_2H_5Br	(0.70)	4.5	0	110	31	24	6.9	1.5228	(37)	18.8	5.6
10	.34	Br[f]	C_2H_5Br	(0.70)	4.5	−20 to −30	120	28	27	7.7	1.5347	(58)	17.6	6.6
11	.10	Br	C_2H_5Br	(0.20)	7.7	0	70	29	27	1.5	1.5281	(46)	5.6	1.6
12	.10	Br	C_2H_5Br	0.18	7.7	−5 to −10	5½	31	25	2.0	1.5241	(39)	5.4	1.6
13	.10	Br	C_2H_5Br	0.16[g]	7.7	−10	20	30	25[t]	2.0	1.5273	(44)	5.9	1.4
14	.10	Br	C_2H_5Br	0.14	7.7	+10	26	31	30	1.8	1.5214	36	5.8	1.6
15	.10	Br	C_2H_5Br	0.15	7.7	30	28	31	29	1.8	1.5161	26	5.9	1.5
16	.10	Br	C_2H_5Br	0.14	7.7	0	35	32	29	1.7	1.5272	(44)	5.8	1.5
17	.10	Br	C_2H_5Br	0.34	7.7	0	30	31	25	1.6	1.5193	(31)	5.8	1.2
18	.10	Br	C_2H_5Br	0.12[h]	7.7	30	11	34	25	1.9	1.5198	31	4.9	1.7
19	.10	Br	C_2H_5Br	0.13[i]	7.7	30	11	32	26	2.2	1.5197	28	5.6	1.4
20	.10	Br	C_2H_5Br	(0.20)[j]	20	30	20	30	21	1.9	1.5177	21	4.9	1.0
21	.10	Br	C_2H_5Br	0.24[k]	50	30	10	30	24	2.0	1.5099	13	5.7	1.0
22	.68	Br	C_2H_5Br	1.00	7.7	30	28	31	27	14.5	1.5158	27	38.2	9.4
23	.10	I[l]	C_2H_5Br	0.13	7.7	0	8	2.5[t]	none	0.5	1.5368	47	10.3	3.2
24	.10	Br	C_2H_5Br	0.14	none[m]	0	22	none	none	14.7[m]	1.4988	trace		0.1
25	.10	Br	C_2H_5Br	0.19[n]	7.7	5	20	none	none	12.7[n]	1.4989	0.3		0.5
26	.10	Br	C_2H_5Br	0.14[o]	7.7	30–40	8	5.4[t]	6[t]	8.0	1.5018	10	2.6	0.9
27	.10	Br	C_2H_5I	0.14	7.7	−5–0	20	31	26	1.9	1.5246	36	5.4	1.6
28	.10	Br	C_2H_5I	0.14	7.7	30	11	32	27	1.9	1.5146	20	5.3	1.8
29	.34	Br	i-C_3H_7Br	(0.70)	4.5	0	60	25	23	11.0	1.5112	13	16.9	5.4
30	.10	Br	t-C_4H_9Br	0.14	7.7	0	20	23	19	5.2	1.5094	10	4.8	0.6
31	.10	Br	C_6H_5Br	0.15	7.7	20	20	32	1.3[t]	5.5	[p]	0	2.6	1.2
32	.10	Br	C_6H_5Br	0.14	7.7	10	12	29[t]	16	2.0	1.5629[p]		5.7	1.7
33	.10	Br	C_6H_5Br	0.14[q]	7.7	0	17	25	17	2.4	1.5650[p]	0	5.3	1.3
34	.10	Br	C_6H_5Br	0.15[q]	7.7	30–35	22	17	4	9.1	1.5642[p]	0	2.5	1.7
35	.34	Br	C_6H_5Br	(0.70)	4.5	0	68	24	6	20.2	1.5620[p]	0	8.0	6.7

[a] Determined by titration except for those values in parentheses which are moles of magnesium and halide employed.

[b] Determined by titration with a standard solution of bromine in carbon tetrachloride, expressing the unsaturation as % anethole; values in parentheses were estimated from the refractive index assuming a linear relationship for mixtures of anethole and *p*-*n*-propylanisole.

[c] Estimated temperature.

[d] Most of the biphenyl was removed by steam distillation, but a small amount was obtained on distillation; total weight 43.5 g. Fraction 2, b.p.150–185° (0.1 mm.) appeared to contain some of the alkylation product corresponding to Fraction 1 of other runs.

[e] In this run the gas evolution during the anethole hydrobromide addition was followed, total volume 2160 cc. corresponding to 85% of theory, after correction to standard conditions.

[f] The anethole hydrobromide was prepared in toluene solution at −55° according to the method of Kharasch and Kleiman and kept at −80° during the addition.

[g] In this run pure sublimed magnesium was used to prepare the Grignard reagent in 95% yield. In some runs commercial magnesium turnings from the Dow Chemical Co. were used, the yield of Grignard reagent being about 77%, and in others an intermediate grade, giving 85% yields of Grignard reagent. Each of these gave similar yields of *meso*-hexestrol dimethyl ether.

[h] The Grignard reagent was filtered through glass wool immediately after preparation.

[i] The Grignard reagent was allowed to settle overnight and the clear supernatant solution was filtered through glass wool.

[j] After addition of the cobaltous chloride, 0.03 mole of ethyl bromide was added to give some "recycling" of the catalyst before adding the anethole.

[k] No "recycling" used here, see *j*; the volume of gas corresponded to 105% of the theoretical.

[l] There was much apparent polymerization of the anethole during addition of the hydrogen iodide.

[m] This was a "blank" run, the usual procedure being followed except that no cobaltous chloride was employed. The product (Fraction 1) corresponded to an 83% yield of the alkylation product IVa.

[n] The ether of the Grignard solution was replaced by benzene before addition of the cobaltous chloride. The product (Fraction 1) corresponded to a 71% yield of the alkylation product IVa.

[o] The Grignard reagent was prepared in di-*n*-butyl ether.

[p] See description of these fractions elsewhere in the experimental section.

[q] The Grignard solution was filtered through glass wool before using.

[r] Yield based in most cases on material melting over about a 1° range near 140–144°.

[s] Yield based in most cases on material melting over a 1–2.5° range in the region of 52–56 5°.

[t] Product was low melting

The combined Fraction 1 from several of the anethole hydrobromide runs with ethylmagnesium bromide (n_D^{25} 1.5276, estimated to contain about 45% of anethole) was fractionally distilled through a 20-cm. Vigreux column, giving the following results:

FRACTION	B.P. °C AT 20 MM.	WT.	n_D^{25}	% ANETHOLE
A	104–108	1.8 g.	1.5052	10
B	108–109	4.5	1.5104	15
C	109–110	2.5	1.5103	16
D	118–119	5.4	1.5344	59
E	119–120	3.4	1.5421	69
F	120–130	1.1	1.5439	63
G	residue	2.3	1.55	

Demethylation of 3.8 g. of Fraction B with hydrobromic-acetic acids and distillation of the phenol gave 2.4 g., b.p. 110–115° (9 mm.). Since this did not crystallize even after redistillation, 0.5 g. was converted to the 3,5-dinitrobenzoate in pyridine solution and fractionally crystallized; 0.33 g. of the 3,5-dinitrobenzoate of *p*-*n*-propylphenol, m.p. 117.5–118.5° was obtained from ethanol. Further recrystallization gave the m.p. 119–119.5°, not depressed by mixing with the authentic sample prepared below.

Demethylation of 3.1 g. of fraction D gave 0.91 g. of phenolic distillate, b.p. 78–118° (8 mm.); 0.5 g. of this was converted to the 3,5-dinitrobenzoate and fractionally crystallized from ethanol. From the least soluble fraction was obtained a small amount of the derivative of *p*-*n*-propylphenol, m.p. 116.5–117.5° (mixed m.p. not depressed) while from the more soluble portion was obtained the derivative of 3-(*p*-hydroxyphenyl)pentane, m.p. 113.5–115° (mixed m.p. unchanged, but depressed below 100° by the derivative of *p*-*n*-propylphenol).

Investigation of Fraction 2 and residues. After removal of the racemic ether from the anethole hydrobromide-ethylmagnesium bromide runs the remainder of Fraction 2 was an oil which could not be further crystallized. Distillation gave fractions b.p. 155–175° (0.2 mm.) and 175–205° (0.2 mm.) which, judging from bromine titrations, may have contained 45% and 80%, respectively, of anethole dimer (isoanethole).

Distillation of the combined residues gave material boiling with decomposition in the range 230–260° (0.6 mm.) which corresponded approximately in molecular weight to a trimer (found mol. wt. 392 using boiling carbon tetrachloride; calc'd for a trimer 444).

Debromination of anethole dibromide. To the stirred mixture of ethylmagnesium bromide (from 0.16 mole of magnesium) and 1 g. of cobaltous chloride was added a solution of anethole dibromide (prepared from 8.5 g. of anethole and 2.95 ml. of bromine in 100 ml. of ether) at 30° over a period of thirty minutes. A vigorous evolution of gas occurred. After hydrolysis, extraction and distillation, 7.8 g. (92%) of anethole was obtained, b.p. 117.5–120° (19 mm.), n_D^{21} 1.5569.

3-(p-Methoxyphenyl)-2-pentene. The Grignard solution from 0.3 mole each of magnesium and ethyl bromide in 250 ml. of ether was slowly treated with 20.2 g. (0.12 mole) of anisoyl chloride in 100 ml. of ether and the mixture was refluxed for six hours. After hydrolyzing and isolating the product, it was distilled with a few crystals of iodine to give 16.4 g. (79%) of the olefin, b.p. 127–132° (19 mm.), n_D^{22} 1.5350. Fractional distillation through a 20-cm. Vigreux column gave material of b.p. 128.5–130° (19 mm.), n_D^{22} 1.5310 [reported (23), b.p. 129–130° at 17 mm., n_D^{21} 1.5395].

3-(p-Methoxyphenyl)pentane. Hydrogenation of 5.7 g. of the pentene was carried out in 50 cc. of absolute alcohol using 0.6 g. of palladium-on-barium sulfate catalyst (24) and thirty pounds pressure, and the process was repeated a second time. The product, 3.6 g. (63%), b.p. 110–112° (10 mm.), n_D^{25} 1.4980, was now saturated to bromine in carbon tetrachloride solution.

This compound was easily prepared in 83% yield by alkylation of anethole hydrobromide with ethylmagnesium bromide in the *absence* of cobaltous chloride (see Table I run 24); b.p. 118–122° (23 mm.), n_D^{25} 1.4988.

3-(p-Hydroxyphenyl)pentane. Demethylation of 2.3 g. of the methyl ether with acetic-hydrobromic acids gave 1.9 g. (90%) of solid upon dilution, m.p. 75.5–76.5°. Recrystallization from petroleum ether raised the m.p. of the phenol to 76.5–77° [reported (25), 79.5–80°].

The *3,5-dinitrobenzoate*, after recrystallization from ethanol, melted at 117–117.5°.

Anal. Calc'd for $C_{18}H_{18}N_2O_6$: C, 60.3; H, 5.1.

Found: C, 60.5; H, 5.1.

p-n-Propylphenol. Anethole (5.8 g.) was hydrogenated using palladium-on-barium sulfate catalyst (24), and the product was shaken with potassium permanganate before distillation, yielding 3.9 g. of *p-n*-propylanisole, b.p. 212.5° (740 mm.), n_D^{25} 1.5024 [reported b.p. 213.5–214.5° at 760 mm. (26), n_D^{20} 1.5040 (27)].

Demethylation of 2.14 g. gave after distillation 1.53 g. of the phenol, b.p. 109–110° (8 mm.), m.p. 16–20°. The *3,5-dinitrobenzoate*, after recrystallization from ethanol, melted at 120–120.5°.

Anal. Calc'd for $C_{16}H_{14}N_2O_6$: C, 58.2; H, 4.3.

Found: C, 58.2, 58.4; H, 4.0, 4.4.

SUMMARY

A detailed investigation has been made of the synthesis of *meso*-hexestrol dimethyl ether from anethole hydrobromide by the cobaltous chloride-catalyzed Grignard procedure. The best yields (31–34%) were obtained using ethylmagnesium bromide.

On the basis of new experimental evidence and previous work on the instability of organo-cobalt compounds, a somewhat different mechanism from that of Kharasch is proposed for cobaltous chloride-catalyzed Grignard reactions. This new mechanism involves the reduction of cobaltous chloride to finely divided cobalt metal as the reactive intermediate in the chain reaction.

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SYNTHESIS OF SOME VICINAL DITHIOLS AND THEIR DERIVATIVES[1]

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The efficacy of BAL (British Anti-Lewisite, 2,3-dimercaptopropanol) in the treatment of arsenical burns and systemic arsenical poisoning has been described in several recent articles (1, 2, 3). Following ghe transmittal of details of the chemistry, preparation, and clinical study of BAL by the British, an intensive program of study was initiated in this country on related compounds with the objective of uncovering more effective and less toxic candidates for antidotal use. This paper deals with that part of the program which aimed specifically at the synthesis of dithiol therapeutic agents. The preparation of a number of dithiols and derived compounds prepared on this program has already been reported (4, 5, 6). These were submitted for pharmacological and physiological tests to several other laboratories working on programs sponsored by the National Defense Research Committee and the Committee on the Treatment of Gas Casualties.

Earlier work by other investigators had indicated that 1,2-dithiols were more efficacious in arsenical therapy than analogs in which the mercapto groups were not on adjacent carbon atoms, and consequently major effort was directed toward the synthesis of the vicinal derivatives. In those cases where a particular functional group imparted some desirable characteristic to the dithiol, as shown by biological tests, homologs of that candidate were prepared, so that structure and efficacy might be further correlated. In Table I are listed the dithiols synthesized along with their significant physical properties.

The classical methods for obtaining thiols failed in many cases to give the desired substituted dithiols and new modifications and methods had to be developed for some of the compounds obtained. Contributing to the difficulties encountered was the instability of 1,2-dithiols, particularly those containing other functional groups. The side reactions encountered were chiefly those involving the elimination of halogen acid or reduction of the dihalide by the thiolating agent.

Thiolations using sodium hydrosulfide under hydrogen sulfide pressure were successful in the preparation of 2,3-dimercaptopropylurethan, 2,3-dimercaptopropylurea, 3,4-dimercaptobutanol, and 2,3-dimercaptopropionaldehyde diethyl acetal from the corresponding dibromides; however, the method failed in most other cases. For example, when applied to the synthesis of dimercaptopropionic acid, dimercaptosuccinic ester, or 2,3-dimercaptobutanol, no dithiols were obtained, but only mixtures of low sulfur content. During attempted isolation

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of several of the BAL analogs which apparently reacted normally with the thiolating agent, loss of thiol titer was experienced through oxidation, dehydration, or dehydrosulfurization. Thus, dibromopropylacetamide reacted with sodium hydrosulfide in methanol at room temperature to give the corresponding dithiol; however, distillation under the mildest conditions resulted in dehydration to a cyclic thioamide believed to be 2-methyl-5-mercapto-Δ^2-dihydrothiazine. The isolation of 3,4-dimercaptobutanol was also complicated by cyclodehydration with formation of what is believed to be 3-mercaptotetrahydrothiophene.

Although dimercaptopropionaldehyde could not be expected to be stable, because of the reactivity of the aldehyde group with the dithiol group, its diethyl acetal was prepared in 90% yield and 92% purity using the sodium hydrosulfide technique. Upon standing at room temperature, the acetal group reacted with the dithiol group with liberation of ethanol to form a polymercaptal; within 48 hours this polymer separated from the purest samples. The sulfur analog of this acetal (2,3-dimercaptopropionaldehyde diethyl mercaptal) could not be prepared by the usual methods because of the instability of the intermediate dibromide; however, reaction of dimercaptopropionaldehyde diethyl acetal with ethyl mercaptan in the presence of acidic catalysts yielded, through mercaptan-acetal interchange, the desired compound. Its instability precluded its biologic evaluation.

Interesting compounds were obtained by modification of BAL and a number of its analogs through formation of derivatives by reaction of the mercapto groups with various reagents. Of the several types examined in this work, stable mercaptoles prepared from acetone and the dithiol are described in this paper. Therapeutic results indicated that the active function, thus covered, was not hydrolyzed *in vivo* and consequently was not available for reaction with the metallic poisons. Use of these compounds was therefore limited to stabilizing the labile dithiol structure while other synthetic operations, ordinarily too drastic, were performed as an attempted route to new dithiols.

EXPERIMENTAL PART

2,3-Dimercaptopropyl acetate. One hundred grams (0.805 mole) of 2,3-dimercaptopropanol (BAL) containing 2 drops of conc'd sulfuric acid in 2 ml. of glacial acetic acid was stirred and maintained at 20–30° by external cooling while 87 g. (0.85 mole) of acetic anhydride was added dropwise during the course of forty-five minutes. The mixture was then heated at 60° for one hour, cooled, and allowed to stand for twenty hours. The crude product was washed with three portions of 250 ml. each of water using ether to break the emulsion. The ether solution was dried over sodium bicarbonate and calcium sulfate and distilled at 0.2–0.3 mm. (bath temperature 125–137°) to yield 94 g. of a colorless oil. This was fractionated through a 20-inch packed column to yield 51 g. (38%) of 2,3-dimercaptopropyl acetate boiling at 90°/1.5 mm. This acetate is a colorless, mobile liquid with a sharp, penetrating odor. It is soluble to the extent of about 1 g. in 100 g. of water, and hydrolyzes rapidly in water. Analyses and physical properties of this compound are given in Table I.

2,3-Dimercaptopropyl propionate. By the same procedure as that described above, 200 g. (1.61 moles) of 2,3-dimercaptopropanol containing 5 drops of conc'd sulfuric acid in 5 ml. of propionic acid was reacted with 260 g. (2.0 moles) of propionic anhydride to give 55 g. (19%) of 2,3-dimercaptopropyl propionate, b.p. 70°/0.2 mm.

2,3-Dimercaptopropyl butyrate. Similarly, 124 g. (1.0 mole) of 2,3-dimercaptopropanol, 7 drops of conc'd sulfuric acid in 5 ml. of butyric acid and 190 g. (1.20 moles) of butyric anhydride were reacted to yield 58 g. (30%) of 2,3-dimercaptopropyl butryate, b.p. 77–78°/0.25 mm.

2,3-Dimercaptopropionaldehyde diethyl acetal. Dibromopropionaldehyde and its diethyl acetal were prepared in 89% and 93% yields respectively following the directions of Grard (7).

Into a 1-liter stainless steel autoclave was charged 150 g. of dibromopropionaldehyde diethyl acetal and a sodium hydrosulfide solution prepared by dissolving 37 g. of sodium in 500 ml. of methanol and saturating the resulting solution at 0° with hydrogen sulfide. The mixture was then shaken under hydrogen sulfide pressure for forty-eight hours at room temperature. The solution was transferred to a 2-liter separatory funnel and saturated with carbon dioxide until the *p*H of the solution was reduced to about 8. The precipitated sodium bicarbonate was dissolved by agitating the solution with 1000 ml. of water, and the oil which separated was extracted with ether. The combined ether extracts were dried over calcium sulfate and after removal of the drying agent, the ether was distilled, leaving a pale yellow oil which analyzed for 29.9% thiol sulfur as compared with 32.68% calculated for dimercaptopropionaldehyde diethyl acetal.

Flash distillation of small portions of the crude acetal served to raise this thiol value slightly. However, polymerization occurred with considerable loss of material. For example, 25 g. of residue remaining after the removal of ether was distilled through a short-path still head at 0.25 mm. from a pot held at 110°. Seventeen grams of distillate was collected which analyzed for 31.2% thiol sulfur or a purity of 95.4% assuming the desired acetal to be the only sulfur component present. Analyses for this fraction are given in Table I.

Upon standing at room temperature for several days, distilled and crude samples of this derivative were observed to separate into two layers; the more viscous layer eventually (two months) became opaque and solid. No odor of hydrogen sulfide was detected in the closed container. The upper layer proved to be ethanol, and the mechanism of decomposition seems clearly to be acetal-mercaptal interchange.

2,3-Dimercaptopropionaldehyde diethyl mercaptal. Attempts to prepare this derivative by the thiolation of the dibromide failed because of the instability of the latter, therefore the following method was used.

Thirty-two grams of dimercaptopropionaldehyde diethyl acetal (92% pure by thiol sulfur analysis) was dissolved in 100 g. of ethyl mercaptan and cooled to −30°. One-half ml. of conc'd hydrochloric acid was added, and after standing at this temperature for one-half hour the mixture was allowed to warm up to 25°. After standing overnight at room temperature the excess ethyl mercaptan was removed by evaporation in a stream of nitrogen. The residue was washed with water and then dried over sodium sulfate. The mercaptal was transferred to a small Claisen flask and distilled at 0.5 mm. Thirteen grams of viscous liquid containing suspended water was collected at 70–100°. The water was removed with sodium sulfate. All attempts to purify this product failed; the analysis in Table I was made on the dried distillate above.

3,4-Dimercaptobutanol. Allyl carbinol was prepared as described by Gilman (8). Bromination of allyl carbinol in chloroform yielded 77% of 3,4-dibromobutanol, b.p. 72–74°/4 mm. (9).

Into a 1-liter stainless steel autoclave was charged 120 g. (0.517 mole) of 3,4-dibromobutanol and a solution of sodium hydrosulfide prepared by dissolving 35 g. of sodium in 500 ml. of methanol and saturating the solution with hydrogen sulfide at 0° The mixture was heated at 40° for forty hours under a hydrogen sulfide pressure of 135 lb./sq. in. The solution was discharged and acidified with 60 ml. of conc'd hydrochloric acid and the precipitated salt removed. After removal of the methanol by distillation under reduced pressure, the residue, consisting of an oil and suspended salt, was shaken with 100 ml. of water and the organic layer separated. The aqueous layer was extracted twice with ether and these

TABLE I

PROPERTIES OF SOME VICINAL DITHIOLS

NAME	FORMULA	PHYSICAL PROPERTIES				ANALYSIS								
						C		H		S		S(H)[b]		Others
		M.P.[a]	B.P.	d_4^{25}	n_D^{25}	Calc'd	Found	Calc'd	Found	Calc'd	Found	Calc'd	Found	
2,3-Dimercaptopropyl acetate	$C_5H_{10}O_2S_2$		90°/1.5 mm.	1.1916	1.5185	36.10	35.4	6.00	6.25	38.60	39.02	38.60	38.20	
2,3-Dimercaptopropyl propionate	$C_6H_{12}O_2S_2$		70°/0.2 mm.	1.1491	1.5089	39.98	40.10	6.66	7.05	35.57	35.53	35.57	35.70	
2,3-Dimercaptopropyl butyrate	$C_7H_{14}O_2S_2$		77–78° 0.25 mm.	1.1095	1.5029	43.28	43.18	7.26	7.45	33.01	32.85	33.01	32.85	
Ammonium 2,3-dimercapto-propionate	$C_3H_9NO_2S_2$	80–85° (dec.)				23.21	23.70	5.84	5.99	41.31	40.50	41.31	41.30	N (Calc'd) 9.02 N (Found) 8.89
2,3-Dimecaptopropylurea	$C_4H_{10}N_2OS_2$	79–81°				28.90	28.77	6.03	6.19	38.57	36.71	38.57	34.40	N (Calc'd) 16.85 N (Found) 16.23
2,3-Dimercaptopropylure-than	$C_6H_{13}NO_2S_2$		129–131° 1.1 mm.	1.1924	1.5277	36.91	36.94	6.72	6.98	32.82	31.99	32.82	32.80	N (Calc'd) 7.17 N (Found) 7.58
3,4-Dimercaptobutanol	$C_4H_{10}OS_2$		96–97°/ 1 mm.	1.1842	1.5583	34.73	35.25	7.29	7.52	46.35	45.97	46.35	45.90	
2,3-Dimercaptopropional-dehyde diethyl acetal	$C_7H_{16}O_2S_2$		dec.			43.09	43.15	8.15	8.01	32.68	31.00	32.68	31.20	
2,3-Dimercaptopropional-dehyde diethyl mercaptal	$C_7H_{16}S_4$		dec.							56.16	49.94	28.08	28.08	

[a] Uncorrected.

[b] Samples of the thiol were titrated in 95% alcohol with 0.1 N I_2 (aq.).

extracts combined with the organic layer. Analysis of an aliquot of this solution indicated the presence of 40 g. (58% theory) of dithiol. The ether was removed by distillation at atmospheric pressure and the product was given a primary distillation, two cuts being collected; one at 40–50°/2.5 mm. and another at 80–100°/1.5 mm. The latter 30 g. was redistilled in a 24" ring-packed column to give 18 g. of pure product boiling at 96–97°/1 mm. The lower-boiling fraction obtained above was redistilled and the main fraction, b.p. 68°/5 mm. had the following analysis:

Found: C, 39.92, 40.15; H, 6.76, 6.73; S, 51.27; S(H), 26.2.

The dehydration product of 3,4-dimercaptobutanol would have the following analysis: Calc'd for $C_4H_8S_2$: C, 39.95; H, 6.66; S, 53.35; S(H), 26.68.

No further characterization of the products was made to determine whether 3-mercaptotetrahydrothiophene or 2-(mercaptomethyl)propylene sulfide resulted from the dehydration.

2,3-Dimercaptopropylurethan. Allylurethan was prepared from allylamine and ethyl chloroformate as described by Bergmann (10). The dibromide was obtained in 87% yield as a low-melting (40–44°) white solid.

A 1-liter stainless steel autoclave was charged with 188 g. (0.65 mole) of 2,3-dibromopropylurethan and a sodium hydrosulfide solution prepared by dissolving 46 g. (2 g.-atoms) of sodium in 450 ml. of methanol and saturating the solution with hydrogen sulfide. The solution was shaken at room temperature for sixteen hours under a hydrogen sulfide pressure of 100 lb./sq.in. After discharging, the solution was acidified with conc'd hydrochloric acid, and the solvent removed by distillation under reduced pressure. The residue of salt and oil was taken up in 200 ml. of water and extracted three times with ether. After drying the ether extracts, the ether was removed and the product distilled in a 4" Vigreux column. Eighty-four grams (65%) of product was collected at 129–131°/1.1 mm. Redistillation in a 24" ring-packed column gave a product with the analyses listed in Table I.

2,3-Dimercaptopropylurea. Dibromopropylurea was prepared according to the method of Taal and Henpel (11). A sodium hydrosulfide solution, prepared by dissolving 41 g. of sodium in 500 ml. of methanol and saturating the solution with hydrogen sulfide at 0°, was charged into a 1-liter Parr bomb with 150 g. of dibromopropylurea. The bomb was agitated under a hydrogen sulfide pressure of 50–75 lb./sq. in. at room temperature for fifty hours and then at 50–60° for an additional two hours. The reaction mixture was acidified with 50 ml. of conc'd hydrochloric acid, and the precipitated salt filtered off. After removing the solvent under reduced pressure at a bath temperature of not more than 60°, the residue of salt and moist product was taken up in 500 ml. of ethyl acetate and 300 ml. of water. The organic solvent layer titrated for 55 g. of dithiol and the water layer for 17 g., assuming only one species to be present. The water layer was extracted four times with a total of 500 ml. of ethyl acetate. This reduced the thiol content to an equivalent of 2.5 g. of dithiol in the aqueous layer. The combined extracts were dried over calcium sulfate, and the solvent removed at reduced pressure. The residue consisted of a pale, pink, viscous syrup, and weighed 85 g. Thiol analysis indicated a purity of 84%.

The impure oil was shaken under nitrogen with 800–850 ml. of warm (35–40°) distilled water; the solution was cooled to room temperature and allowed to settle. The cloudy solution was decanted from undissolved oil (18 g.), shaken with 20 g. of acid-extracted kieselguhr, and filtered by suction. The clear filtrate was rapidly stirred while cooling in a mixture of Dry-Ice-methanol until it solidified. The solid cake containing crystals of the desired product in fine dispersion was allowed to warm up to the melting point, and the crystals removed. Thirty-six grams of product was obtained which analyzed for 36.2% thiol sulfur, corresponding to a purity of 94%. Analyses are given in Table I.

Further purification of 2,3-dimercaptopropylurea was not generally possible, although crystallization of small amounts was effected in isolated cases. A sample which analyzed for 99% of the theoretical thiol sulfur (m.p. 79–81°) was obtained from ethanol-ether mixtures but when this technique was applied to the purification of larger or less pure samples, only oils were obtained.

The synthesis of 2,3-dimercaptopropionic acid and its methyl ester is outlined elsewhere (5). Several derivatives of these compounds not previously described are as follows:

4-Carboxy-2,2-dimethyl-1,3-dithiolane was prepared by refluxing 15 g. of the 2,3-dimercaptopropionic acid in 100 ml. of dry acetone for 0.5 hour. After removal of excess acetone, the product was distilled, b.p. 121–122°/1.5 mm., or crystallized directly from petroleum ether (b.p. 30–75°) to yield 18 g. (93%), m.p. 51–53°. Neut. equivalent, calc'd: 178.3; found, 182.

4-Carbomethoxy-2,2-dimethyl-1,3-dithiolane, the acetone mercaptole of methyl 2,3-dimercaptopropionate was prepared by mixing 114 g. of methyl 2,3-dimercaptopropionate and 46 g. of acetone, cooling to 0° in an ice-bath, and saturating the solution with dry hydrochloric acid. An aqueous layer separated and was removed after the solution had warmed to room temperature. The product was washed twice with water and then with dilute sodium bicarbonate solution. After drying, it was distilled through a 4" Vigreux column, b.p. 73–74°/0.5 mm., yield 110 g. (82%). By reaction with ammonia in alcohol solution, this derivative was converted into the corresponding amide, *4-carbamyl-2,2-dimethyl-1,3-dithiolane*, m.p. 89–90°.

Anal. Calc'd for $C_6H_{11}NOS_2$: C, 40.68; H, 6.23; S, 36.17; N, 7.90.
Found: C, 40.14; H, 6.75; S, 36.75; N, 7.87.

This amide was also prepared from 4-carboxy-2,2-dimethyl-1,3-dithiolane (above) by reaction of 12 g. (0.087 mole) with 2.6 g. (0.044 mole) of urea at 160–170° for one hour. The resultant viscous mass was crystallized from benzene to yield 3 g. (25%) of product, m.p. 89–90°. There was no depression of the melting point when this compound was mixed with the 4-carbamyl-2,2-dimethyl-1,3-dithiolane prepared from the ester (above).

Ammonium 2,3-dimercaptopropionate. Thirty-five grams of dimercaptopropionic acid was dissolved in 200 ml. of ether and cooled to 0°. Ammonia gas was bubbled into the solution until no further precipitation occurred. One-half of the ether was removed by evaporation on a steam-bath and enough absolute alcohol was added (about 120 ml.) to just dissolve all the solid. On cooling, the product crystallized as white flakes; these were filtered off and dried *in vacuo* yielding 36 g. (93%) of slightly hygroscopic crystals which melted (with decomposition) between 80° and 85°. See Table I for analyses.

SUMMARY

1. A number of vicinal dithiols, analogs of BAL (British Anti-Lewisite), have been prepared and their properties recorded.

2. Several new derivatives of vicinal dithiols are reported.

WILMINGTON, DEL.

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[CONTRIBUTION FROM THE INSTITUTE OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF SZEGED]

ADDITION OF MALEIC ANHYDRIDE TO ANETHOLE. II.

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Received August 2, 1948

In a previous paper we reported (1) that anethole with maleic anhydride forms a bis-adduct, the properties of which are in best agreement with the spatial formula I and naturally also with its enantiomorphic form. We can use as a simpler manner of design formula II which represents together the two enantiomorphic members of the racemate.

This formula is in close analogy with formula III which Wagner-Jauregg (2) first suggested for the bis-adduct formed by the addition of maleic anhydride to 1,1-diphenylethylene. The same formula was also accepted by Bergmann and co-workers (3), who even generalized it for other bis-adducts formed by the action of maleic anhydride on 1,1-diarylethylene derivatives, doing this in spite of the fact that they had not decisively proved the correctness of this formula. It is remarkable that in the meantime Wagner-Jauregg himself (4) had repudiated formula III. One of Wagner-Jauregg's essential arguments against the correctness of formula III was the failure of his efforts to prove the olefinic linkages revealed by this structure, *e.g.*, finding the bis-adduct resistant to catalytic hydrogenation. Indeed, we also observed that the olefinic bonds shown by our formula I could not be demonstrated by the simplest usual reactions for these linkages. So, *e.g.*, although the chloroform solution of our bis-adduct readily absorbs bromine (5), which is, however, finally due to a substitution, as we could isolate from the inhomogeneous oily reaction product only a very small amount of a crystalline product, containing at most one atom of bromine per mole of the initial substance; our bis-adduct does not give a color reaction with tetranitromethane, and resists catalytic hydrogenation (Pt or Pd) at atmospheric pressure.[1]

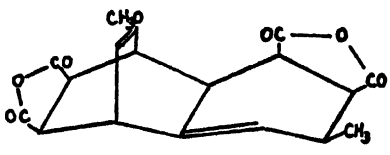
In spite of these negative results, we finally succeeded in a different way in showing both the olefinic bonds revealed by our formula I. Thus, the correctness of this formula is only now completely proved, because in our earlier paper (1) no argument was advanced in favor of the olefinic bond not belonging to the enol ether group.

The presence and position of one of the two olefinic bonds was proved earlier by the enol ether character of the bis-adduct. We tried first to locate the other olefinic bond by bromination of the hydroxy lactone tricarboxylic acid ("B-acid", IV) obtained from the bis-adduct. We found that IV, treated in aqueous solution with potassium hypobromite, or in methanolic solution with bromine, gave a monobromo product, yielding with diazomethane a monobromo tetramethyl ester[2] (m.p. 242°) for which we must accept formula Vb. It is therefore clear that the initially-formed dibromo addition product instantly loses one mole

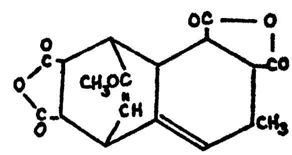
[1] No experiments were made under pressure.

[2] As shown in our previous paper (1) on the action of diazomethane, the lactone ring of IV split off, yielding the keto tetracarboxylic acid tetramethyl ester Va.

of hydrogen bromide, which leads to the formation of Vb. As the selective bromination by bromosuccinimide (6) of ester Va leads to another monobromotetracarboxylic keto acid tetramethyl ester (m.p. 153–158°, obviously Vc) than that mentioned above, it follows that free bromine did not act as a substituent on one of the hydrogen atoms attached to the neighboring carbon atom of the lactonized or free carbonyl group.



I



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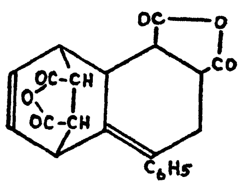
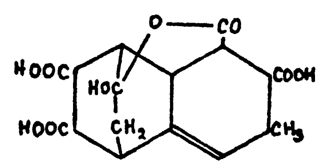
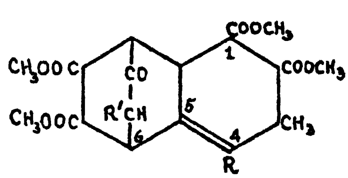


III



IV

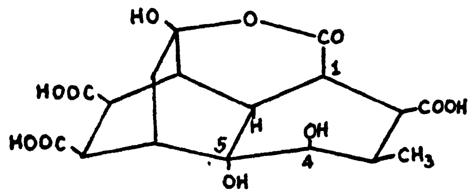


V

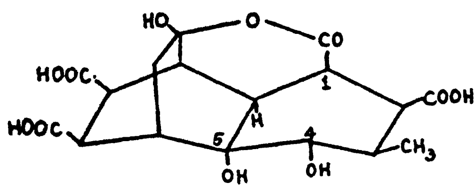
a. R = R′ = H
b. R = Br, R′ = H
c. R = H, R′ = Br

The olefinic linkage of IV and Va could be more clearly demonstrated by the products obtained through conversion with hydrogen peroxide. However, we found here a phenomenon of isomerism, whose exact explanation needs further investigation. On study of spatial models, we came to the conclusion that the addition of two hydroxyl groups to IV is only possible in the manner shown by formulas VI and VII, *i.e.*, the hydroxyl group in position 5 must have a trans position in relation to the carboxyl groups, whereas the hydroxyl group in position 4 can be either in a cis (VI) or a trans (VII) position. The only possibility for the trans position of the hydroxyl group attached to carbon atom 5 results from the fact that the endo-ethylene bridge permits only the existence of a cis-decalin type. It is to be expected that VI can easily, even spontaneously, undergo a rearrangement, followed by an intramolecular condensation leading to VIIIa. Indeed, we found that in acetic acid medium, on the action of hydrogen peroxide,

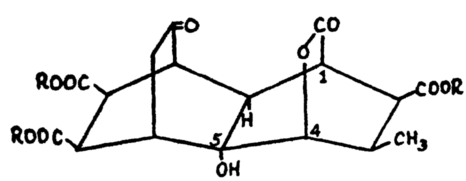
from IV ($C_{17}H_{18}O_9$) the product $C_{17}H_{18}O_{10}$, m.p. 327–330°, is formed, in the sense of equation: $C_{17}H_{18}O_9 + H_2O_2 = C_{17}H_{18}O_{10} + H_2O$. This product, which is sparingly soluble in water and almost insoluble in the usual organic solvents, behaves on direct titration like a tribasic acid, corresponding to the lactonic character shown in formula VIIIa. Likewise, in the sense of equation $C_{21}H_{26}O_9 + H_2O_2 = C_{20}H_{24}O_{10} + CH_3OH$, treating Va ($C_{21}H_{26}O_9$) with hydrogen peroxide gave a neutral trimethyl ester (m.p. 265–270°), the analytical data of which agreed with those required by formula VIIIb. Actually, we could not decide whether this ester is the ester of the hydroxytricarboxylic keto acid VIIIa, for the latter could not be esterified because of its insolubility; on the other hand, the ester decomposed on saponification.



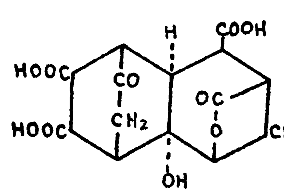
VI



VII



VIII. a. R=H; b. R=CH₃



IX

Furthermore, the conversion of IV with hydrogen peroxide led to still another product (m.p. 305–306°), in addition to the above-mentioned lactone. The analytical data of this other product agreed with those required by formula VI

or VII ($C_{17}H_{20}O_{11}$). It was readily soluble, even in cold water, and behaved on direct titration like a tribasic acid. For this product formula VII can be excluded, as on treatment with diazomethane it did not form a tetramethyl ester[3] but led to a neutral trimethyl ester ($C_{20}H_{24}O_{10}$), whose identity with VIIIb (obtained from Va by treatment with hydrogen peroxide) could not be determined beyond doubt. It is possible that the structure of the easily-soluble product obtained by the action of hydrogen peroxide on IV is not the type of glycol corresponding to formula VI, but represents a lactone, or even a mixture of two isomeric lactones of formula $C_{17}H_{18}O_{10}$ containing one mole of crystal water. This is revealed by the fact that at 100° *in vacuo* it quickly loses one mole of water with destruction of its crystals, giving a hygroscopic substance. Concerning its structure, formula IX seems not to be probable, as such a ring structure would possess appreciable strain, so that the spontaneous lactonization could be explained only with difficulty.

The complete elucidation of the structures of both of the lactones mentioned above requires further investigation, the more so as it is possible that the easily-soluble lactone is a mixture of isomers. In spite of this, it is certain that the formation of the above-described substances shows the presence of an olefinic linkage in the initial compound. Thus, in IV the only unsaturated bond, and also two of them in the bis-adduct, are demonstrated.

EXPERIMENTAL

4-Bromo derivative of the keto tetracarboxylic acid tetramethyl ester Va (Vb). A. *From the B-acid (IV) with potassium hypobromite.* To a solution of 6.3 g. of bromine in 60 ml. of 10% aqueous solution of caustic soda, a solution of 3.64 g. of the B-acid (IV) in 200 ml. of a 2% aqueous solution of caustic soda was added. After standing for two days at room temperature, 88% of the active bromine was used up, and a negligible amount of precipitate appeared, which was filtered off. The filtrate was treated with sodium sulfite, then after acidifying (*p*H 1–2) with 2 *N* hydrochloric acid, evaporated *in vacuo* to dryness. The solid residue was twice boiled with 25 ml. of anhydrous methanol, and the solution thus obtained evaporated at reduced pressure. The yellow, oily residue crystallized from 20 ml. of water (charcoal) in colorless needles which were several times recrystallized from water, yielding 1.6 g. of a product containing bromine; m.p. 196°. As the analysis showed that this product consisted of a mixture of partially esterified derivatives of the monobromo acid, a sample (0.4 g.) was completely esterified by treatment of its anhydrous methanolic solution with diazomethane in the customary manner. The tetramethyl ester[3] thus obtained was recrystallized, first from methanol, then from ethyl acetate, yielding colorless needles, m.p. 237–238°. The substance contained bromine (Beilstein).

Anal. Calc'd for $C_{21}H_{25}BrO_9$: C, 50.31; H, 5.01.

Found: C, 49.98, 50.15; H, 5.04, 4.99.

B. *From the B-acid (IV) with bromine in methanolic solution.* To a solution of 4 g. of the B-acid in 15 ml. of anhydrous methanol, 35 ml. of a 5% solution of bromine in anhydrous methanol was added. The color of the bromine disappeared in a few minutes. On evaporation, a yellowish oil was obtained, which after triturating with 12 ml. of water and standing for a few hours became mostly crystalline. After removing the supernatant aqueous layer, the oily-crystalline product was boiled for a few minutes with 100 ml. of water, then the small undissolved part filtered, and the filtrate, after concentration to 30 ml., allowed to stand at room temperature until crystallization became complete. Thus 1.1 g. of colorless needles was obtained which had the m.p. 183–184°. As analysis showed that this product

consisted of a mixture of partially esterified derivatives of monobromo-IV, its total esterification was carried out using diazomethane. Thus, from 1 g. of the previously mentioned product, 0.7 g. of the same bromo trimethyl ester was obtained; m.p. 236–237°, which rose to 242° by recrystallization from ethyl acetate; m.p. of a mixture with a specimen obtained through method A, 238°. The substance contained bromine (Beilstein).

Anal. Calc'd for $C_{21}H_{25}BrO_9$: C, 50.31; H, 5.01.
Found: C, 50.11; H, 5.22.

θ^1-Bromo derivative of the keto tetracarboxylic acid tetramethyl ester Va (Vc). A solution of 1 g. of the ester Va and of 0.6 g. of bromosuccinimide in 60 ml. of tetrachloromethane was refluxed for 15 minutes, whereby precipitation of succinimide took place. On evaporating the filtrate an oily residue was obtained, which readily crystallized when triturated with cold methanol. The bromine-containing product was recrystallized from methanol, m.p. 153–158° (dec.).

Anal. Calc'd for $C_{21}H_{25}BrO_9$: C, 50.31; H, 5.01.
Found: C, 50.21; H, 5.25.

Reaction of the B-acid (IV) and of its methylated derivative (Va) with hydrogen peroxide. The sparingly soluble lactone (VIIIa). To a solution of 1.9 g. of the B-acid (IV) in 50 ml. of warm (80°) glacial acetic acid, 22 ml. of 33% hydrogen peroxide solution was added drop by drop within thirty minutes. The mixture was kept at 80° for another thirty minutes, then concentrated *in vacuo* to 6 ml. On standing for twelve hours, crystallization took place, yielding 1.5 g. of a colorless product, the main part of which dissolved on boiling for a short time with 10 ml. of water. The solution thus obtained contains the readily soluble lactone. The insoluble remainder was recrystallized once from 35 ml. of water. The colorless prisms showed no decomposition even on drying at 100° *in vacuo* over P_2O_5; yield 0.2 g., m.p. 327–330° (dec.). In the usual organic solvents the substance was practically insoluble even on boiling.

Anal. Calc'd for $C_{17}H_{18}O_{10}$: C, 53.40; H, 4.74.
Found: C, 53.58, 53.67; H, 4.88, 5.07.

Titration.[3] Calc'd for 3 COOH groups:[4] COOH, 35.34. Found: COOH, 34.95.

The readily-soluble lactone ($C_{17}H_{20}O_{11}$). After treatment with charcoal, the aqueous solution of the easily-soluble part of the crude reaction product previously described was kept in the ice-chest for some hours and the deposited prisms recrystallized twice from a small amount of water. For analysis, the substance was dried at room temperature in a desiccator over calcium chloride for twelve hours; no destruction of the crystals was observed; m.p. 305–306°.

Anal. Calc'd for $C_{17}H_{20}O_{11}$: C, 51.00; H, 5.03.
Found: C, 50.93, 50.86; H, 4.99, 5.23.

Titration.[3] Calc'd for 3 COOH groups:[4] COOH, 33.74. Found: COOH, 33.48.

On drying the substance (0.1 g.) *in vacuo* at 100° over P_2O_5, loss of one mole of water per mole of substance took place within two hours, accompanied by destruction of the crystals. The substance thus obtained was hygroscopic; on further drying, a slower loss of weight was observed.

Esterification of the readily-soluble lactone with diazomethane. A solution of 0.1 g. of the readily-soluble lactone in 2 ml. of anhydrous methanol was treated with diazomethane in the usual manner. On concentrating the solution to 0.5 ml., colorless prisms separated, which were recrystallized once from dilute methanol; m.p. 235–240°.

Anal. Calc'd for $C_{20}H_{24}O_{10}$: C, 56.58; H, 5.70.
Found: C, 56.62, 56.68; H, 5.87, 5.93

Trimethyl ester VIIIb. To a solution of 2.1 g. of ester (Va) in 25 ml. of glacial acetic

[3] All carboxyl estimations were carried out by direct titration of the hot alcoholic-aqueous solution of 30–50-mg. samples using 0.05 N sodium hydroxide and phenolphthalein.

[4] For the fourth (lactonized) carboxyl group, the lactone titrations did not give correct results, as the substance decomposed on boiling with dilute sodium hydroxide.

acid, 25 ml. of a 21% hydrogen peroxide solution was added, and the precipitate was redissolved by heating the mixture to 90°. After keeping the mixture at this temperature for ninety minutes, on cooling, 0.25 g. of colorless needles separated. On evaporating the filtrate at reduced pressure, an oily-crystalline residue was obtained, the oily part of which could be removed by solution in methanol. The crystalline residue (0.2 g.) proved to be identical with the primarily isolated crystal substance. The united crops were recrystallized from water, then dried *in vacuo* at 110°; m.p. 265–270° (dec.), after softening at 250°.

Anal. Calc'd for $C_{20}H_{24}O_{10}$: C, 56.58; H, 5.70.

Found: C, 56.76, 56.57; H, 5.93, 5.89.

Although the form of the crystals and their solubility seem to differ from those of the product obtained from the readily-soluble lactone by the action of diazomethane, it is possible that the two substances are identical, taking into account the possibility that they may consist of mixtures containing two isomeric lactones in different proportions. This conclusion can be deduced from the fact, that in spite of their correct analytical data, both products show unsharp m.p.'s, furthermore that their mixture melts at 236°, not showing a depression in relation to the lower-melting specimen. Accepting this conclusion, it follows that the readily-soluble lactone also consists of a mixture of isomers.

SZEGED, HUNGARY

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A SYSTEM CORRELATING MOLECULAR STRUCTURE OF ORGANIC COMPOUNDS WITH THEIR BOILING POINTS. VII. NEW BOILING POINTS FOR CERTAIN PARAFFINS AND OLEFINS[1]

CORLISS R. KINNEY AND WILLIAM L. SPLIETHOFF

Received August 16, 1948

In 1938 a method was devised for calculating the boiling points of organic compounds from their structure (1). The method was based on the boiling points of hydrogen and the normal paraffin hydrocarbons, all other organic compounds being considered to be derivatives of these. Since then, several new methods have been published for obtaining the boiling points of hydrocarbons (2). In addition to these, which are limited to hydrocarbons, Klages has developed a general method very similar to the Kinney method (3).

In 1940, the boiling points of all of the paraffins whose atmospheric boiling points had been recorded were compared with the calculated values (4). Out of 108 paraffins, ten were found whose observed boiling points differed from the calculated by more than 10°. Since then, Butler (5) has resynthesized the third paraffin on this list, 2,4,6-trimethylheptane, and obtained the value 147.6° which is well within the 10° limit. Irving[2] has also prepared this hydrocarbon and obtained similar results. Consequently, this hydrocarbon should be removed from the list.

The boiling point of the fourth paraffin, 4,5-dimethyloctane, was incorrectly abstracted (6) and Francis[3] was the first to call attention to this error. The correct boiling point given by Festracte (7) was 160.5° which differs from the calculated by only 0.5°. Therefore, this hydrocarbon should be stricken from the list. The tenth paraffin, 4,8,12-trimethylhexadecane, should also be removed because it was subsequently shown that this hydrocarbon, crocetane, actually had 20 carbon atoms (8) instead of 19 for which the above structure was assigned. Using the new structure the calculated boiling point is 332.2° compared with the observed value of 334.0°.

Of the remaining seven paraffins the four appearing in Table I, numbers 5, 6, 7, and 9, have been resynthesized. The boiling points of all of these come well within the 10° limit and may, also, be removed from the original list.

The eighth paraffin on the list, 6-methyl-7-ethyldodecane, was prepared by Karrer (9) at the same time as the seventh and ninth hydrocarbons appearing in Table I. Since all three of Karrer's boiling points were uncorrected for barometric pressure and, apparently, for exposed thermometer thread as well, it seemed highly probable that the corrected boiling point of 6-methyl-7-ethyldodecane approximates the calculated value fairly closely as do 4-methyl-6-propyl-

[1] Presented at the New York meeting of the American Chemical Society, September 15, 1947.

[2] Lee Irving, University of Utah, 1943.

[3] Francis, private communication.

hendecane and 6-propyldodecane which were resynthesized. Therefore, it appears that 6-methyl-7-ethyldodecane should also be stricken from the 1940 list.

The two remaining paraffins, 3-methyl-3-ethylpentane and 2,3-dimethyl-3-ethylpentane,[4] constitute a separate case. 3-Methyl-3-ethylpentane was resynthesized by Barrowman,[5] but the same observed boiling point was obtained. Since this is 11.6° above the calculated value, the whole series of 3,3-disubstituted paraffins has been reexamined.

The calculated and observed boiling points of these hydrocarbons are given in Table II. It will be observed that the usual close agreement is obtained for the 3,3-dimethyl derivatives, but that markedly exalted boiling points are given by the 3-methyl-3-ethyl and the 3,3-diethyl derivatives. This exaltation of the boiling point is in sharp contrast with the depression in boiling point shown by 2,2-dimethyl derivatives for which a b.p.n. was assigned. In a similar way it is now proposed to assign a b.p.n. of 1.0 to account for the high boiling points

TABLE I

BOILING POINTS OF PARAFFINS 5, 6, 7, AND 9

NO.	STRUCTURE	BOILING POINT, °C.		
		Old Obsv'd	Calc'd	New Obsv'd
5	2,4,5,7-Tetramethyloctane	210.0	192.2	186.3
6	2,5,9-Trimethyldecane[a]	207.0	218.0	211.1
7	4-Methyl-6-propylhendecane	233.5[b]	249.6	242.6
9	6-Propyldodecane	242.0[b]	254.5	251.6

[a] 2,5,9-Trimethyldecane is better nomenclature than 2,6,9-trimethyldecane.
[b] 729 mm.

of the 3-methyl-3-ethyl and the 3,3-diethyl structures. Thus, when calculating boiling points of compounds containing these groupings a b.p.n. of 1.0 should be added. In this way, the newly calculated boiling points appearing in Table II were obtained. It will be observed that the new values are in much better agreement with the observed boiling points. The first member of the 3,3-diethyl series shows an unusually high deviation (7.7°) but probably this is due to the discrepancy often shown by the first members of series.

The high boiling points of 3-methyl-3-ethyl and 3,3-diethyl derivatives may be observed in other series of compounds, as for example, 4-methyl-4-ethyl-1-hexene (3-methyl-3-ethyl-5-hexene) among the olefins. Using the b.p.n. of 1.0 for the 3-methyl-3-ethyl grouping, the calculated boiling point comes within +1.7° of the observed instead of −7.2° without it.

Just what effect the 4-methyl-4-ethyl and 4,4-diethyl structures have on the boiling point is uncertain because no boiling points of these derivatives have been reported. The effect of the 4,4-dipropyl and 5,5-dibutyl structures is also unknown.

[4] This hydrocarbon appears on the 1940 list as 2,2-dimethyl-3-ethylpentane, but is an typographical error.

[5] S. R. Barrowman, University of Utah, 1944.

The normal boiling points of a number of new paraffins have been reported in the literature since 1940. Only four of these deviate from the calculated value by more than 10°. They are 2,4-dimethylnonane (10), 2,7-dimethyl-4,5-diethyloctane (11), 6,8-dimethyltridecane (12), and 2,2,3,3,4-pentamethylpentane (13). The deviations are respectively −10.3°, −11.3°, −18.1°, and +16.5°. Pressure and temperature corrections were not applied to the observed boiling points of the first two hydrocarbons; consequently, it seems quite likely that the corrected boiling points of these two hydrocarbons would fall well within the 10° limit. On the other hand, the boiling points of 6,8-dimethyltridecane

TABLE II

Boiling Points of 3,3-Distributed Paraffins

HYDROCARBONS	BOILING POINTS, °C.		
	Old Calc'd	Obsv'd	New Calc'd
3,3-Dimethylpentane	82.8	86.1[a]	
3,3-Dimethylhexane	110.6	112.0[a]	
3,3-Dimethylheptane	136.2	137.3[a]	
3,3-Dimethyloctane	160.0	161.2	
3-Methyl-3-ethylpentane	107.2	118.3[a]	116.7
2,3-Dimethyl-3-ethylpentane	130.8	142.0[a]	139.7
3-Methyl-3-ethylhexane	133.1	143.0[a]	141.9
3-Methyl-3-ethylheptane	157.1	163.9[b]	165.3
3-Methyl-3-ethyloctane	179.6	185.7[c]	187.3
3,3-Diethylpentane	129.9	146.5[a]	138.8
3,3-Diethylhexane	154.1	162.7[c]	162.4
3,3-Diethylheptane	176.9	186.7[c]	184.6
3,3-Diethyloctane	198.1	205.1[c]	205.5
3,3-Diethylnonane	218.3	222.1[c]	225.3

[a] A.P.I. Research Project 44, "Selected Values of the Properties of Hydrocarbons", Tables 2a, 3a, and 4a (1945), values to the nearest tenth of a degree.
[b] Previously reported as 156.3° by Campbell and Eby, *J. Am. Chem. Soc.*, **62**, 1800 (1940).
[c] Boiling points of new paraffins; see the Experimental Part.

and 2,2,3,3,4-pentamethylpentane vary considerably from the calculated and consequently the cause of this deviation should be investigated.

A reexamination of the olefins on the 1940 list (4) gave results similar to those obtained for the paraffins. 3-Decene,[6] 5-decene (14), and 4,8-dimethyl-4-nonene have been resynthesized. The new observed boiling points are given in Table III.

2,3-Dimethyl-2-butene (15)[6] and 2,3,5-trimethyl-2-hexene (16) have also been resynthesized, with little change of the boiling point in the first case, but with an increase of 12.3° in the latter. These hydrocarbons are members of the 2,3-dimethyl-2-olefin series and in addition to these members, the whole series has been resynthesized up to 2,3-dimethyl-2-octene (16). On reexamining the data available for all the $R_2C = CR_2$ olefins, it was found that raising the b.p.n.

[6] F. K. Balli, University of Utah, 1943.

for this type of olefin linkage from 2.8 to 3.2 brought the boiling points of all of the known members of the series well within the 10° limit. In view of these new data, it is recommended that the b.p.n. of the tetrasubstituted double bond be raised to 3.2.

2,2-Dimethyl-4-ethyl-3-hexene was found to be another incorrectly abstracted compound on consulting the original paper (17). The correct structure was 4,4-dimethyl-3-ethyl-2-pentene and the calculated boiling point for this structure agrees very well with the observed boiling point, although the observed range of 8° makes the true boiling point rather uncertain.

The first three olefins of the 1940 list, 3-methylene-2,2,4-trimethyl-4-ethylhexane, 3-methylene-2,2,4,4-tetramethylhexane, and 3-methylene-2,2,4,4,5-pentamethylhexane[7] may be considered to be examples of hydrocarbons in which four or more alkyl groups are attached to adjacent carbon atoms of the main chain of six carbon atoms (4). These structures were assigned the b.p.n. of 1.0. If this b.p.n. is used in calculating the boiling points of the methylene derivatives, the deviations of the observed boiling points from the calculated

TABLE III

NEW BOILING POINTS FOR RESYNTHESIZED OLEFINS

OLEFIN	CALC'D B.P.	NEW OBSV'D B.P.	DEVIATION
3-Decene....	171.3	173.3	+2.0
5-Decene....	171.3	169.6	−1.7
4,8-Dimethyl-4-nonene....	184.6	182.3	−2.3

become −1.0°, +3.2° and −1.0° respectively. If the same b.p.n. is also applied to the fourth olefin on the list, 4-methylene-3,3,5,5-tetramethylheptane, for which there are no paraffinic analogs, its calculated boiling point comes within 5.4° of the observed value. Consequently, it seems very likely that this b.p.n. should be used in calculating the boiling points of olefins with bunched side chains such as these, even though the side chains may be partly alkenyl radicals. If this is done, one of the known olefins, 3-methylene-2,2,4-trimethylhexane, has a calculated boiling point of 158.8° as compared with an observed boiling range of 146–150°. Although the mid-point of this range is more than 10° from the calculated, the 10° limit comes within the observed boiling range and it is not considered likely that the true boiling point of this compound is too far from the calculated. It should also be pointed out that the first compound on the 1940 list, 3-methylene-2,2,4-trimethyl-4-ethylhexane, is an example of a 3-methyl-3-ethyl hydrocarbon for which an additional b.p.n. of 1.0 should be added. The use of this additional b.p.n. brings the calculated boiling point to within 1.0° of the observed value.

The two remaining olefins on the list, 2,4,6-trimethyl-3-heptene and 2,4,7-trimethyl-4-octene, were prepared by Tuot (18). The boiling point of the second

[7] This nomenclature is employed because "the longest chain in the molecule must be used in calculating the boiling point," ref. 4, p. 559.

of these, 2,4,7-trimethyl-4-octene, comes within the 10° limit if the reported boiling point is corrected for the low observed pressure. The first hydrocarbon, 2,4,6-trimethyl-3-heptene, was resynthesized[8] and the new observed boiling point also fell within the prescribed limit, 148.2° as compared with 156.2°.

Since 1940, boiling points for a number of new olefins have appeared. Five of these have boiling points deviating by more than 10° from the calculated. For two of them, 5,5-dimethyl-3-heptene (19) and 2,2,3,4,5,5-hexamethyl-3-hexene (20), boiling ranges of 8° and 13° respectively were reported, and in view of the uncertainty regarding their true normal boiling points the reported ranges are of little value. Also, 2,5-dimethyl-4-hendecene (21) was reported as being impure; consequently, the true boiling point of this hydrocarbon is uncertain. The fourth olefin, 2,2,5-trimethyl-3-hexene (22), and the fifth, 2,2,5,5-tetramethyl-3-hexene (13), have observed boiling points of 11.1° and 14.7° lower respectively than the calculated values, taking into consideration the 2,2-dimethyl structures occurring in both of them. Since these hydrocarbons have related structures it may be possible that their structure requires a b.p.n. to account for the abnormally low boiling points which have been reported. Further verification of these boiling points should be made, however.

TABLE IV

NEW 3,3-DISUBSTITUTED PARAFFINS

	Analysis Calc'd C	Calc'd H	Found C	Found H	B.P. at 760 mm., °C.	n_D^{20}	d_4^{20}
3-Methyl-3-ethylheptane	84.5	15.5	84.4	15.4	163.9	1.4205	0.7478
3-Methyl-3-ethyloctane	84.6	15.4	84.1	15.5	185.7	1.4250	.7528
3,3-Diethylhexane[a]	84.5	15 5	84 4	15.1	162.7	1.4261	.7624
3,3-Diethylheptane	84.6	15.4	84.2	15.4	186.7	1.4299	.7703
3,3-Diethyloctane	84.7	15.3	84.4	15.5	205.1	1.4321	.7713
3,3-Diethylnonane	84.8	15.2	84.5	15.4	222.1	1.4365	.7758

[a] Valentine and Spliethoff, The Pennsylvania State College, 1948.

In view of the several methods that have been developed for the prediction of the boiling points and other physical properties of compounds, particularly hydrocarbons, values reported on the literature should be very carefully checked before publication. Relatively simple calculations may save other investigators a great deal of time.

EXPERIMENTAL

The methods of making the hydrocarbons described below are only briefly outlined since no unusual procedures or modifications were used. Some of the data were abstracted from theses completed at the University of Utah and in these cases the boiling points were corrected for exposed thermometer stem. Pressures were held at 760 mm. ± 1 mm. by added

[8] Lento and Spliethoff, The Pennsylvania State College, 1948.

air pressure from a ballast tank, excepting for the boiling points of 3-methyl-3-ethylpentane and 3-decene which were corrected for low barometric pressure by the method of Hass and Newton (23).

The remaining boiling points were obtained on one degree (or less) fractions using a 35-plate column, 12 mm. by 40 cm. and packed with $\frac{1}{16}$-inch stainless steel helices. The boiling points were determined in a modified semimicro Cottrell boiling point apparatus (24). Pressures were maintained at 760 mm. ± 0.05 mm. and temperatures were read with an accuracy of ±0.2° using a calibrated copper-constantan thermocouple.

The refractive indices were measured with a Bausch and Lomb Abbé-type refractometer. The compensating prisms of this instrument were calibrated by the manufacturer to give values at the wave length of the sodium D-line. The sample prisms were maintained at a temperature of 20.0° ± 0.1° by circulating water from a constant-temperature bath. The scale readings were calibrated against a standard test plate having a refractive index of 1.5137 supplied with the instrument.

Densities were measured in a Nicol type pycnometer that had been calibrated to four decimal places with an uncertainty of ±0.0001 using distilled water as the calibrating medium. The pycnometer was placed in a constant-temperature bath maintained at 20.0° ± .05°. After twenty minutes, the volume of liquid was adjusted to the calibration mark and allowed to come to room temperature. All weighings were made on a magnetically-damped analytical balance which had been calibrated and adjusted against a set of weights certified by the National Bureau of Standards. The weights used were also calibrated against the same standard set using the same balance.

2,4,6-Trimethylheptane.[3] Diisobutyl ketone was treated with methylmagnesium iodide, giving methyl diisobutyl carbinol. On distillation at normal pressure, the carbinol dehydrated to the corresponding olefin, which was reduced with sodium and alcohol until a negative test for unsaturation was obtained with alkaline permanganate. The product, 2,4,6-trimethylheptane, boiled at 145.6–146.1° (corr.) at 760 mm. ± 1 mm. The index of refraction was n_D^{20} 1.4209.

2,4,5,7-Tetramethyloctane.[2] 2-Chloro-4-methylpentane was treated with sodium in the Wurtz reaction. The product, 2,4,5,7-tetramethyloctane, boiled at 186.2–186.3° (corr.) at 760 mm. ± 1 mm. The index of refraction was n_D^{20} 1.4229.

2,5,9-Trimethyldecane.[9] Chloroacetone was treated with two equivalents of isoamyl magnesium bromide, giving 2,5,9-trimethyl-5-decanol, which was dehydrated. The olefin was hydrogenated in a Parr machine with Adams catalyst to yield 2,5,9-trimethyldecane which boiled at 211.1° at 760 mm. The index of refraction was n_D^{20} 1.4244 and the density was d_4^{20} 0.7546.

Anal. Calc'd for $C_{13}H_{28}$: C, 84.8; H, 15.2.
Found: C, 84.6; H, 15.2.

4-Methyl-6-propylhendecane. 4-Methyl-6-propyl-6-hendecanol was prepared following Karrer's method (9). After dehydrating the alcohol, the olefin was hydrogenated in a Parr machine with Adams catalyst. 4-Methyl-6-propylhendecane had the boiling point 242.6° at 760 mm. The index of refraction was n_D^{20} 1.4389 and the density d_4^{20} 0.7798.

Anal. Calc'd for $C_{15}H_{32}$: C, 84.9; H, 15.1.
Found: C, 84.7; H, 14.6.

6-Propyldodecane.[10] 6-Propyl-6-dodecanol was prepared using Karrer's directions (9). This was dehydrated to the corresponding olefin which distilled at 244.6–245.6° (corr.) at 643.8 mm. The index of refraction was n_D^{23} 1.4405 and the density was d_4^{23} 0.7791. The olefin was reduced with sodium and alcohol until a negative test for unsaturation was obtained with alkaline permanganate. A fraction boiling at 240–242° at 649.7 mm. was redistilled at 760 mm. ± 1 mm. and boiled at 250.6–252.6° (corr.). The index of refraction was n_D^{18} 1.4332 and the density was d_4^{19} 0.7721.

[9] M. L. Briggs, Nancy Hoeflich, and W. L. Spliethoff, The Pennsylvania State College, 1944.

[10] J. R. Morandi, University of Utah, 1943.

3-Methyl-3-ethylpentane.[5] 3-Methyl-3-ethylpentane was synthesized from 3-chloro-3-methylpentane and diethylzinc (25). Its boiling point was 118.8° (corr.), the index of refraction was n_D^{20} 1.4089, and the density d_4^{20} 0.7230.

3,3-Disubstituted paraffins. The following new 3,3-disubstituted paraffins given in Table II were made by reacting a tertiary halide with a primary alkyl Grignard reagent (26). The boiling points were determined in the modified semimicro Cottrell apparatus (24) as described above. Their physical properties are given in Table IV.

3-Decene.[6] 3-Decene was prepared by the method of Schmidt and Boord (27) for making hexenes. α,β-Dibromobutyl ethyl ether was made from butyraldehyde using Swallen and Boord's procedure (28) for α,β-dibromoethyl ethyl ether. After washing the crude product with water and drying with calcium chloride, it was treated with *n*-hexylmagnesium bromide. The crude product of this reaction, α-hexyl-β-bromobutyl ethyl ether, was refluxed with *n*-propyl alcohol and zinc dust for 14.5 hours. The filtrate from this reaction was poured into cold water. The olefin was dried and distilled from sodium. On fractionation, a cut boiling at 173.0–173.5° (corr. 760 mm.) was collected as 3-decene. The index of refraction was n_D^{20} 1.4221 and the density was d_4^{20} 0.7447.

4,8-Dimethyl-4-nonene. 2-Methyl-1-pentanol was oxidized to 2-methylpentanal which was treated with isoamylmagnesium bromide. The resulting carbinol was dehydrated with fused potassium acid sulfate and the olefin distilled from sodium. Fractionation in the 35-plate column yielded a cut which boiled at 182.3° at 760 mm The index of refraction was n_D^{20} 1.4329 and the density d_4^{20} 0.7567.

Anal. Calc'd for $C_{11}H_{22}$: C, 85.7; H, 14.3.
Found: C, 85.4; H, 14.5.

2,3-Dimethyl-2-butene.[6] This olefin was prepared by dehydrating dimethylisopropylcarbinol with anhydrous oxalic acid. The carbinol was made from acetone and isopropylmagnesium bromide. After distilling from sodium the olefin was fractionated through a ten plate column and the fraction boiling at 68.0–68.7° at 645.8 mm. was taken as the heart cut. The boiling point at 760 mm. was calculated by the method of Hass and Newton (23) to be 72.75–74.45° or 74.1° for the midpoint.

2,4,6-Trimethyl-3-heptene.[3] This olefin was prepared by the dehydration of 2,4,6-trimethylheptanol-4 with potassium acid sulfate. The tertiary alcohol was prepared from isobutylmagnesium bromide and methyl isobutyl ketone. After refluxing the olefin with sodium, it was fractionated in a semimicro column packed with $\frac{1}{16}$-inch stainless steel helices. Two fractions, boiling from 145–148°, were selected as the heart cut. The boiling point at 760 mm. was found to be 148.2°, the index of refraction was n_D^{20} 1.4201 and the density was d_4^{20} 0.7366.

Anal. Calc'd for $C_{10}H_{20}$: C, 85.7; H, 14.3.
Found: C, 85.3; H, 14.5.

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SUMMARY

The boiling points of ten paraffins not agreeing with the calculated boiling point have been reexamined. All of these have been corrected excepting two which are 3-methyl-3-ethyl and 3,3-diethyl paraffins. Additional new members of these series have been synthesized, and it has been established that these paraffins have abnormally high boiling points. Therefore, a boiling point number has been assigned these structures.

Also, the boiling points of 12 olefins not in agreement with the calculated

values have been reexamined. New boiling points published for olefins containing the tetrasubstituted double bond require that the boiling point number of this linkage be raised from 2.8 to 3.2. All of the remaining olefins have been accounted for by literature correction, new boiling points, or by the application of paraffin boiling point numbers. Two new olefins, 2,2,5-trimethyl-3-hexene and 2,2,5,5-tetramethyl-3-hexene, appear to have abnormally low boiling points.

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[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

REACTIONS OF ATOMS AND FREE RADICALS IN SOLUTION. XVI. THE REACTION OF ALLYL BROMIDE WITH BROMOTRICHLOROMETHANE

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The addition of carbon tetrachloride and bromotrichloromethane to allyl chloride has been investigated (1). With carbon tetrachloride a number of substances were obtained. From the chlorine analyses and the molecular weights of the several fractions, it was estimated that the one-to-one (B), the two-to-one (D) and the higher polymerization products are formed in the approximate ratio 1:8:4. These materials are assumed to be formed by the following series of reactions:

$$CCl_4 \xrightarrow{CH_3\cdot} CH_3Cl + \cdot CCl_3$$

1. $CH_2{=}CHCH_2Cl + \cdot CCl_3 \longrightarrow CCl_3CH_2\dot{C}HCH_2Cl$ (A)

2. $(A) + CCl_4 \longrightarrow \underset{(B)}{CCl_3CH_2CHClCH_2Cl} + CCl_3\cdot$

3. $(A) + CH_2{=}CHCH_2Cl \longrightarrow CCl_3CH_2\underset{\underset{\displaystyle CH_2\dot{C}HCH_2Cl}{|}}{C}HCH_2Cl$ (C)

4. $(C) + CCl_4 \longrightarrow CCl_3CH_2\underset{\underset{\displaystyle CH_2CHClCH_2Cl}{|}}{C}HCH_2Cl$ (D) $+ CCl_3\cdot$

5. $(C) + (CH_2{=}CHCH_2Cl)_n \longrightarrow [(C) + (CH_2{=}CHCH_2Cl)_n]$

5a. $[(C) + (CH_2{=}CHCH_2Cl)_n] + CCl_4 \longrightarrow [(C) + (CH_2{=}CHCH_2Cl)_n]Cl + Cl_3C\cdot$

On the other hand, with bromotrichloromethane the reaction indicated in step 2 takes place readily, and the only product of the reaction is a one-to-one adduct.

When allyl bromide is treated with an excess of bromotrichloromethane, practically none of the one-to-one adduct, ($CCl_3CH_2CHBrCH_2Br$), of bromotrichloromethane and allyl bromide is obtained. The reaction mixture after removal of the reactants consisted of equimolar quantities of the following two compounds:

$$\underset{(E)}{BrCH_2CHBrCH_2Br} \text{ and } \underset{(F)}{Cl_3CCH_2CHBrCH_2CCl_3}$$

At first glance, the formation of products (E) and (F) appears most startling. However, the formation of these products is easily explained on the basis of the

following series of reactions:

6. $BrCCl_3 \xrightarrow{h\nu} Br\cdot + \cdot CCl_3$

7. $CH_2{=}CHCH_2Br + \cdot CCl_3 \longrightarrow CH_2{=}CHCH_2CCl_3 + Br\cdot$ (G)

$\qquad \searrow CCl_3{-}CH_2\dot{C}HCH_2Br$

$\qquad \downarrow$ (H)

$\qquad CCl_3CH_2CH{=}CH_2 + Br\cdot$ (G)

8. $CH_2{=}CHCH_2Br + Br\cdot \rightarrow BrCH_2\dot{C}HCH_2Br$ (I)

9. (H) + $CH_2{=}CHCH_2Br \rightarrow$ (G) + (I)

10. $BrCH_2\dot{C}HCH_2Br + BrCCl_3 \rightarrow BrCH_2CHBrCH_2Br + \cdot CCl_3$
(I) (E)

11. $CCl_3CH_2CH{=}CH_2 + \cdot CCl_3 \rightarrow CCl_3CH_2\dot{C}HCH_2CCl_3$
(G) (J)

12. (J) + $BrCCl_3 \rightarrow Cl_3CCH_2CHBrCH_2CCl_3 + \cdot CCl_3$
(F)

We are uncertain, at this time, whether product (G), namely 4,4,4-trichloro-1-butene, is formed by direct displacement of a bromine atom by the free trichloromethyl radical, by the addition of this free radical to the allyl bromide followed by elimination of a bromine atom,[1] or by interaction of (H) with allyl bromide to give (G) and (I) as indicated in step 9.

It is obvious, from a consideration of reactions 6 to 12 inclusive, that if instead of an excess of bromotrichloromethane one uses an excess of allyl bromide, that products (G), (4,4,4-trichloro-1-butene) and (E) (1,2,3-tribromopropane) should be the major reaction products. This was found to be the case.

The structure of 4,4,4-trichloro-1-butene was determined by ozonolysis of the compound, and identification of the formaldehyde and of the trichloropropionaldehyde. The latter compound, when treated with 2,4-dinitrophenylhydrazine, is first converted into dichloroacrolein, which then condenses with the 2,4-dinitrophenylhydrazine. The melting point of this substance was not depressed by the addition of an authentic sample of the 2,4-dinitrophenylhydrazone of β,β-dichloroacrolein.

EXPERIMENTAL

Photochemical addition of bromotrichloromethane to allyl bromide. A solution of allyl bromide, free of peroxides, (0.2 mole) and bromotrichloromethane (0.8 mole) was maintained at 25° in a water-bath and internally illuminated with a mercury vapor-neon fluores-

[1] The mechanism of this reaction is under investigation in this laboratory.

cent coil for 46 hours while a slow stream of nitrogen gas was passed through the solution. At the end of that time, no allyl bromide or other olefins could be demonstrated in the solution. The unreacted bromotrichloromethane was removed from the reaction mixture at 55 mm. pressure, and the residue was subjected to distillation at low pressure. The following fractions were collected:[2] Fraction I: 23 g.; b.p. 40–44° at 0.05 mm.; n_D^{20} 1.5767. Fraction II: 2.5 g.; b.p. 44–61° at 0.05 mm.; n_D^{20} 1.5589. Fraction III: 26.5 g.; b.p. 61–63° at 0.05 mm.; n_D^{20} 1.5456. Residue: 3.2 g.

Anal. Fraction I. Calc'd for $C_3H_5Br_3$: C, 12.83; H, 1.79; Mol. wt. 280.8; Ag. eq. 93.6.
Found: C, 13.42; H, 1.75; Mol. wt. 283; Ag. eq. 84.3.

These data suggested that Fraction I was 1,2,3-tribromopropane mixed with a small quantity of the compound of Fraction III. For this reason, about 20 g. of this material was carefully redistilled at low pressures, and about 10 g. of material collected which had the index of refraction 1.5840 at 20°, and the melting point 15–16°. The melting point of this material was not depressed by admixture with an equal quantity of an authentic sample of 1,2,3-tribromopropane. The rest of the distillate had the index 1.5830 at 20°.

From the analyses of Fraction III it appears to be a hexachlorobromopentane contaminated with small quantities of 1,2,3-tribromopropane.

Anal. Fraction III. Calc'd for $C_5H_5Cl_6Br$: C, 16.79; H, 1.41; Ag. eq. 51.1 Mol. wt. 358.
Found: C, 16.43; H, 1.52; Ag. eq. 52.2; Mol. wt. 344.

Fraction II is probably a mixture of 1,2,3-tribromopropane and the hexachlorobromopentane.

Identification of fraction III, (1,1,1,5,5,5-hexachloro-3-bromopentane). The structure of the 1,1,1,5,5,5-hexachloro-3-bromopentane was established by the following series of reactions:

1. $Cl_3CCH_2CHBrCH_2CCl_3 \xrightarrow{KOH} Cl_3CCH_2CH{=}CHCCl_3 + KBr$

   $\searrow^{KOH}$ $CCl_3CCH_2CHBrCH{=}CCl_2$ (small amount)

2. $CCl_3CH_2CH{=}CHCCl_3 \xrightarrow[\text{Hydrol.}]{O_3} CCl_3CH_2CHO + Cl_3CCHO$

3. $Cl_3CCHO + H_2NNHC_6H_3(NO_2)_2 \rightarrow Cl_3CCH{=}NNHC_6H_3(NO_2)_2$

4. $Cl_3CCH_2CHO \rightarrow Cl_2C{=}CHCHO + HCl$

5. $Cl_2C{=}CHCHO + NH_2NHC_6H_3(NO_2)_2 \rightarrow Cl_2C{=}CHCH{=}NNHC_6H_3(NO_2)_2$

A mixture of 19 g. of Fraction III and 3.2 g. of potassium hydroxide in 60 ml. of absolute alcohol was allowed to stand for 24 hours at room temperature. The reaction mixture was then cooled, and the solid which separated (5.1 g.) was collected. The alcohol was removed from the filtrate at reduced pressure and the residue thus obtained was dissolved in ether, washed with water, and the ether solution dried with sodium sulfate. The residue was subjected to distillation at low pressures. The following fractions were collected: Fraction I: 1.2 g.; b.p. 39–40° at 0.03 mm.; n_D^{20} 1.5330; Ag. eq. 56.5; Mol. wt. 255. Fraction II: 0.45 g.; b.p. 40–44° at 0.03 mm.; n_D^{20} 1.5350. Fraction III: 8 g., b.p. 75–76° at 0.04 mm.; n_D^{20} 1.5413.

The analysis and the molecular weight of Fraction III indicate that it is a pure sample of 1,1,1,5,5,5-hexachloro-3-bromopentane.

Anal. Calc'd for $C_5H_5Cl_6Br$: Ag. eq. 51.1; Mol. wt. 358.
Found: Ag. eq. 51.3; Mol. wt. 357.

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[2] To prevent superheating of the material, a slow stream of nitrogen gas was used. The bubbles produced were extremely small.

Fraction I (Mol. wt. 255) was dissolved in ethyl acetate, and ozone was passed through the solution. Upon removal of the solvent at reduced pressure, 45°, water was added to the residue, and the whole was heated on a steam-bath for 2.5 hours, and then allowed to cool. The water layer was separated from the oil layer by filtration through a filter paper wet with water, and treated with an alcoholic solution of 2,4-dinitrophenylhydrazine. The precipitate which separated was boiled with a few ml. of absolute alcohol. The compound decomposed at 305–306° (unc.). The decomposition point of the 2,4-dinitrophenylhydrazone of chloral is recorded in the literature to be 315°.

The alcoholic filtrate (after removal of the 2,4-dinitrophenylhydrazone of chloral) was allowed to cool. A solid, which upon crystallization melted at 159°, separated. This material was the 2,4-dinitrophenylhydrazone of β,β-dichloroacrolein (1).

Peroxide-induced addition of bromotrichloromethane to allyl bromide. A solution of allyl bromide (0.3 mole) and bromotrichloromethane (1 mole) was heated to 70° in a flask equipped with a reflux condenser and stirrer. Acetyl peroxide (0.8 g.), dissolved in bromotrichloromethane (0.4 mole) was slowly added to the reaction mixture (45 min). The whole mixture was then maintained at 70° for ten hours. At that time no test for allyl bromide could be demonstrated in the solution. The reaction mixture was worked up in a manner similar to that described for the light-induced addition of bromotrichloromethane to allyl bromide.

Only two products were isolated, namely 1,2,3-tribromopropane and 1,1,1,5,5,5-hexachloro-3-bromopentane. Furthermore from a comparison of the index of refraction of the reaction mixture and the curve of the index of refraction of the pure 1,2,3-tribromopropane, and pure 1,1,1,5,5,5-hexachloro-3-bromopentane, it would appear that at most only insignificant quantities of the adduct of bromotrichloromethane and allyl bromide are formed in the reaction.

Photochemically-induced reaction of bromotrichloromethane and allyl bromide in the presence of an excess of the latter reagent. A solution of freshly distilled allyl bromide (1.1 mole) and bromotrichloromethane (0.33 mole) was maintained at 30–40° and internally illuminated with a mercury vapor-neon fluorescent coil for eleven hours. The air in the apparatus was displaced by nitrogen.

Most of the unreacted allyl bromide was removed by distillation at ordinary temperatures. The residue was distilled through a Vigreux column (6″), and the following fractions were collected: Fraction I: 25.5 g.; b.p. 36–43° at 0 04 mm.; n_D^{20} 1.5681. Fraction II. Material which collected in cold-trap (CO_2) 65.2 g.; n_D^{20} 1.4895. Residue, 1 g. Fraction I has been demonstrated to be a mixture of four parts of 1,2,3-tribromopropane and one part of the "dimer" of allyl bromide (2). The material caught in the cold-trap was fractionated at ordinary pressure, and the fraction boiling at 123–131° was collected. Upon distillation of this material the fraction boiling at 128–129° was collected. This material had the index of refraction 1.4678 and was considered to be pure 4,4,4-trichloro-1-butene.

Anal. Calc'd for $C_4H_5Cl_3$: C, 30.1; H, 3.15; Ag. eq. 53.2.

Found: C, 29.6; H, 3.22; Ag. eq. 53.6.

Identification of the structure of 4,4,4-trichloro-1-butene ($C_4H_5Cl_3$).

$$1.\ Cl_3CCH_2CH{=}CH_2 \xrightarrow[\text{Hydrol.}]{O_3} Cl_3CCH_2CHO + CH_2O$$

$$2.\ Cl_3CCH_2CHO \xrightarrow{H_2NNHC_6H_3(NO_2)_2} Cl_2C{=}CHCH{=}NNHC_6H_3(NO_2)_2$$

The material ($C_4H_5Cl_3$) (6.9 g.) was dissolved in ethyl acetate cooled to −70°, and ozone (8%) was passed through the mixture, until no further absorption took place. The solvent was removed at room temperature, and the ozonide was decomposed by warming with water on a steam-bath (3 hours). The layers were separated, and the water layer discarded. The oil layer was mixed with an alcohol-water solution of 2,4-dinitrophenylhydrazine and warmed for 15–30 minutes. Upon cooling, a solid separated, which was crys-

tallized twice from small quantities of alcohol. The melting point of the substance from the second crystallization was 158–159°, indicating that it was the 2,4-dinitrophenylhydrazone of β,β-dichloroacrolein. The material did not depress the melting point of an authentic sample of the 2,4-dinitrophenylhydrazone of β,β-dichloroacrolein (1).

Another sample of the compound $C_4H_5Cl_3$ was dissolved in carbon tetrachloride and ozonized at −12°. The liberated formaldehyde was caught in two tubes containing water. Upon addition of a methanol solution of methone to the contents of the two tubes a heavy precipitate resulted. This material melted at 189.5°, which indicates that it is a quite pure sample of the methone derivative of formaldehyde.

SUMMARY

1. In photochemical or peroxide-induced reactions of allyl bromide and an excess of bromotrichloromethane the products are 1,2,3-tribromopropane and 1,1,1,5,5,5-hexachloro-3-bromopentane.

2. In photochemical or peroxide-induced reactions of bromotrichloromethane and an excess of allyl bromide, the products are 1,2,3-tribromopropane and 4,4,4-trichloro-1-butene.

3. The structures of the new compounds formed have been determined by conventional methods.

4. A mechanism which accounts for the products formed is suggested.

CHICAGO 37, ILL.

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[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

REACTIONS OF ATOMS AND FREE RADICALS IN SOLUTION. XVII. DECOMPOSITION OF DIACETYL PEROXIDE IN ALLYL BROMIDE[1]

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The unusual behavior of allyl bromide with bromotrichloromethane (1) to give (as the main reaction products) 4,4,4-trichloro-1-butene and 1,2,3-tribromopropane,

$$CH_2 = CHCH_2Br + BrCCl_3 \xrightarrow[\text{Perox.}]{h\nu} Cl_3CCH_2CH = CH_2 + BrCH_2CHBrCH_2Br$$

prompted us to investigate the decomposition of diacetyl peroxide in allyl bromide.

RESULTS

When diacetyl peroxide dissolved in allyl bromide is added dropwise to excess boiling allyl bromide, a slow decomposition ensues. About one mole of carbon dioxide is formed per mole of peroxide. It is most interesting, however, that no methane and very little methyl bromide are formed in this reaction. The following products were isolated in the amounts indicated per mole of diacetyl peroxide:

1. 1-Butene (25.7 g., 0.459 mole; 46% of the calculated amount, on the basis of equation 2);
2. Methyl bromide (5.2 g., 0.055 mole);
3. 1,3-Dibromopropane (4.5 g., 0.22 mole);
4. An unidentified strongly lachrymatory material containing bromine; apparent molecular weight 166 (2.2 g.);
5. A dimer of allyl bromide (4-bromomethyl-5-bromo-1-pentene) (44 g., 0.182 mole);
6. 1,5-Dibromo-2-bromomethylpentane (?) (5.6 g., 0.017 mole);
7. A polymer of the consistency and color of pitch (72 g.).

DISCUSSION

The formation of compounds 1 to 7 may be accounted for on the basis of the following series of reactions:

[1] The authors wish to acknowledge the generous support of the Firestone Tire and Rubber Company which made this research possible.

1. $(CH_3COO)_2 \xrightarrow{\Delta} CH_3\cdot + CO_2 + CH_3COO\cdot$

2. $CH_2{=}CHCH_2Br + CH_3\cdot \rightarrow \underset{(A)}{CH_3CH_2{-}\dot{C}HCH_2Br} \rightarrow CH_3CH_2CH{=}CH_2 + Br\cdot$

$$\searrow \quad CH_2{=}CHCH_2CH_3 + Br\cdot$$

2A. $A + CH_2{=}CHCH_2Br \rightarrow CH_3CH_2CH{=}CH_2 + BrCH_2\dot{C}HCH_2Br$

3. $CH_2{=}CHCH_2Br + Br\cdot \rightarrow \underset{(B)}{BrCH_2\dot{C}HCH_2Br}$

4. $\underset{B}{BrCH_2\dot{C}HCH_2Br} + CH_2{=}CHCH_2Br \rightarrow \begin{array}{l} BrCH_2CHCH_2Br \\ \quad | \\ \quad CH_2 \\ \quad | \\ \quad HC\cdot \\ \quad | \\ \quad CH_2Br \end{array} \text{(C)}$

$$\swarrow \qquad\qquad\qquad\qquad \downarrow$$

$$\begin{array}{l} BrCH_2CHCH_2Br \\ \quad | \\ \quad CH_2 \\ \quad | \\ \quad HC{=}CH_2 \end{array} + Br\cdot \qquad\qquad \underset{(D)}{\begin{array}{l} BrCH_2CHCH_2Br \\ \quad | \\ \quad CH_2 \\ \quad | \\ \quad HC{=}CH_2 \end{array}} + Br\cdot$$

5. $(C) + CH_2{=}CHCH_2Br \rightarrow (D) + (B)$

6. $\underset{(B)}{BrCH_2\dot{C}HCH_2Br} + \text{Hydrogen donor} \rightarrow \underset{(E)}{BrCH_2CH_2CH_2Br}$

7. $(C) + \text{Hydrogen donor} \rightarrow \underset{(F)}{\begin{array}{l} BrCH_2CHCH_2CH_2CH_2Br \\ \qquad | \\ \qquad CH_2Br \end{array}}$

8. $(C) + CH_2{=}CHCH_2Br + \xrightarrow{(CH_3COO)_2} \text{Polymer}$

9. $(D) + CH{=}CHCH_2Br \xrightarrow{(CH_3COO)_2} \text{Polymer}$

10. $\cdot CH_3 + \text{Bromine donor} \rightarrow CH_3Br$

It is rather uncertain whether in step 2 the free methyl radical first adds to the allyl bromide molecule, with decomposition of the newly formed free radical to 1-butene and a bromine atom, or whether the free methyl radical attacks the allyl bromide molecule displacing a bromine atom and forming 1-butene. The fact that methyl radicals attack butyl chloride and crotyl chloride (2) to give pentane and 2-pentene would indicate that such a displacement reaction is possible, whereas we have not had any evidence as yet of an addition of a free methyl radical to a double bond of an aliphatic olefin. An alternative suggestion for the formation of 1-butene and (B) is offered in 2A. Similarly, there is uncertainty concerning the mechanism of formation of (D). This substance could

be formed by a displacement mechanism (step 4) or an addition mechanism followed either by disproportionation (step 4), or interaction with a molecule of allyl bromide (step 5) to give (D) + (B).

The products (E) and (F) probably result from abstraction of hydrogen atoms from some molecules by the free radicals (B) and (C), respectively. The free radical (B), is obviously the precursor of all of the brominated substances isolated in this reaction.

PROOF OF STRUCTURE OF REACTION PRODUCTS

The 1-butene and the 1,3-dibromopropane were identified by the usual methods (see experimental part). The structure of the dimer of allyl bromide (D) (4-bromomethyl-5-bromo-1-pentene) was established by degradation and synthesis (Fig. 1).

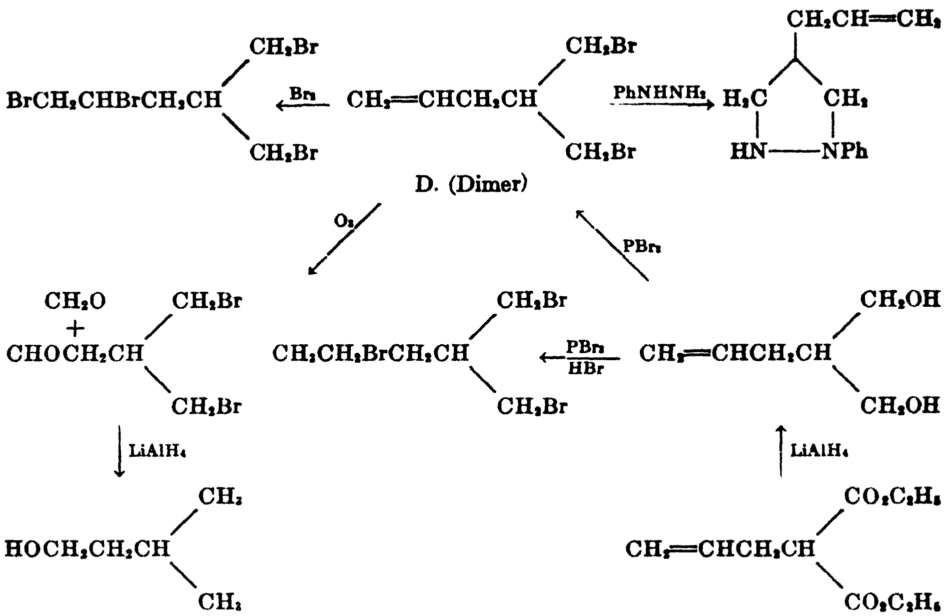

FIG. 1

Establishment of Identity of Dimer (4-Bromomethyl-5-bromo-1-pentene)

The structure of compound (F) (1,5-dibromo-2-bromomethylpentane) was not definitely established. The analytical data agree well with this structure. Furthermore, because of formation of 1,3-dibromopropane (step 6), there is strong presumptive evidence that the free radical (C) can also abstract a hydrogen atom to give 1,5-dibromo-2-bromoethylpentane (step 7).

EXPERIMENTAL

Allyl bromide, Eastman's pure grade, was distilled through a Vigreux column (b. 71.3°) and was free of peroxides.

Decomposition of diacetyl peroxide in allyl bromide. A solution of diacetyl peroxide (33.5

g., 0.284 mole) in allyl bromide (50 g.) was added dropwise (through a capillary tube which projected below the surface of the liquid) to allyl bromide (183 g.) contained in a 500-cc. flask, which was immersed in an oil-bath held at 90°. The gaseous products of the reaction were passed through an efficient reflux condenser, attached directly to the reaction flask, and into a gas-absorption train, consisting of a trap cooled with ice-salt mixture, a second trap immersed in a Dry Ice-acetone bath, three U-tubes filled with soda-lime, and a fourth with calcium chloride. The gases not absorbed by the soda-lime were collected over water in a special gas-collection apparatus.

The addition of the diacetyl peroxide required 6 hours. Carbon dioxide (10.9 g.; 0.25 mole) was the only non-condensible gas formed in the reaction. The contents of the first trap (14 g.) were distilled at normal pressure through a Vigreux column; 13.6 g. of allyl bromide was obtained. The residue (about 0.9 g.) was mostly acetic acid, which was confirmed by the fact that the residue gave a lanthanum nitrate test. The material which had collected in the Dry Ice-acetone cold-trap was allowed to distill at room temperature and again condensed in a cold-trap. The material was thus separated into two fractions: allyl bromide and the material (8.7 g.) which collected in the cold-trap. To ascertain the butene content of this material three grams of it was mixed with 20 cc. of chloroform and cooled with a Dry Ice-acetone mixture. A solution of bromine in chloroform which contained 211.3 mg. of bromine per cc. was then added dropwise. When 7170 mg. of bromine (34 cc.) had been taken up the solution turned yellow, indicating that the mixture contained 84% of butene. The other material in the butene was shown to be methyl bromide by absorbing the butene in sulfuric acid and determining the molecular weight of the unabsorbed gas. The value obtained was in excellent agreement with that calculated for methyl bromide. The total amount of methyl bromide formed is, however, small (1.5 g.).

Further to identify the butene formed in the reaction, the dibromide prepared as described above was carefully purified by distillation at reduced pressure. A colorless material boiling at 55°/15 mm. was thus obtained (d_4^{20} 1.7984; n_D^{20} 1.5152). These values agree well with those of a synthetic sample of 1,2-dibromobutane: b.p. 55°/15 mm.; d_4^{20} 1.7951; n_D^{20} 1.5149. The yield of butene (on the basis of equation 2) was 46%.

The main reaction mixture was dark brown. It was distilled at reduced pressure. The following fractions were collected: Fraction 1, unchanged allyl bromide; Fraction 2, b.p. 58–95°/23 mm., 9.5 g.; Fraction 3, b.p. 95–108°/23 mm., 12.5 g.; Residue, black solid resembling heavy tar, 20.5 g.

Fraction 2 was purified by distillation through a Vigreux column. Two fractions were obtained. The fraction boiling at 43–45°/15 mm. (1 3 g) was identified as 1,3-dibromopropane (n_D^{20} 1.5237).

Anal. Calc'd for $C_3H_6Br_2$: Br, 79.2. Found: Br, 78.9.

The fraction boiling at 55–60°/20 mm., n_D^{20} 1.4760, (2.2 g.) is probably a mixture. The apparent molecular weight of the material was 166. Because the analyses for carbon, hydrogen, and bromine were inconsistent (C, 24.76 and 26.89; H, 3.05 and 3.47; Br, 57.73 and 51.95); and because it decomposed violently when heated, the study of this mixture was not pursued further. The substance when first isolated liberated iodine from potassium iodide solution.

Fraction 3 was distilled through a Vigreux column, and the fraction (12.5 g.) which boiled at 93–95°/15 mm. was collected (n_D^{20} 1.5256). This fraction was shown to be a dimer of allyl bromide, namely, 4-bromomethyl-5-bromo-1-pentene.

Anal. Calc'd for $C_6H_{10}Br_2$: C, 29.8; H, 4.14; Br, 66.19; mol. wt., 242.
Found: C, 29.4; H, 3.91; Br, 66.3; mol. wt., 244.

The black residue was ground in a mortar and extracted with chloroform. The chloroform was removed, and the remainder was distilled in a Hickman flask at 0.01 mm. pressure (temperature of bath 85–90°). The material had the index of refraction 1.5672 at 20°. This substance is probably 2-bromomethyl-1,5-dibromopentane [compound (F) in the theoretical part of the paper].

Anal. Calc'd for $C_6H_{11}Br_3$: Br, 74.3; mol. wt., 323.
Found: Br, 74.2; mol. wt., 321.

The residue remaining in the Soxhlet apparatus was dried *in vacuo* at 80° and analyzed. Found: C, 51.7; H, 3.89; Br, 40.8.

It was insoluble in all common organic solvents.

Proof of structure of dimer of allyl bromide—4-bromomethyl-5-bromo-pentene-1. (a) *Presence of a double bond.* The dimer (1.9858 g.) was dissolved in 10 cc. of carbon tetrachloride and treated with a solution of bromine in carbon tetrachloride (1 cc. of CCl_4 sol. contained 36.8 mg. of Br_2). After the addition of 36 cc. of the bromine solution, the reaction mixture turned yellow. The calculated amount of bromine solution for one double bond is 35 cc. To isolate the adduct, the volatile solvents were first removed, and the residue was distilled in a Hickman flask at 0.02 mm. pressure and a bath temperature of 150°. The index of refraction of the material thus obtained was 1.5909 at 20°.

Anal. Calc'd for $C_6H_{10}Br_4$: C, 17.9; H, 2.5; Br, 79.6; mol. wt., 402.
Found: C, 17.6; H, 2.2; Br, 79.8; mol. wt., 404.

(b) *Position of the double bond in the dimer, and its skeletal structure.* The position of the double bond was determined by ozonolysis. The substance (1 g.) was dissolved in 20 cc. of carbon tetrachloride and cooled to 0°, and a stream of ozone (4.5% O_3) was passed through the mixture for 20 minutes. The volatile materials were collected in two test tubes each containing 20 cc. of water. The water solutions were combined and treated with 5 cc. of saturated water solution of methone. Within a few minutes a crystalline material had separated. This was collected and dried, m.p. 189°, which was not depressed by admixture with a very pure synthetic sample of the formaldehyde methone compound (m.p. 191°). The yield of formaldehyde was 32% of the calculated amount. In an investigation of this method, it has been shown (3) that the optimum yield of formaldehyde by this process is about 35% of the calculated value.

The carbon tetrachloride was removed from the "ozonized" sample at reduced pressure. The ozonide which remained was a colorless oil. In order to decompose it, it was treated with 20 cc. of water, and the whole was heated on a steam-bath for one hour. The reaction mixture was extracted four times with small amounts of ether; the ether extracts were combined, washed with a cold solution of sodium bicarbonate, dried with sodium sulfate, and filtered. The ether was removed from the filtrate, and the residue distilled in a Hickman flask at 15 mm. pressure. The material which boiled at 130° (temperature of the oil-bath) was collected. The material gave the characteristic reactions of an aldehyde. Thus, it gave a 2,4-dinitrophenylhydrazone (m.p. 158°), a positive test with $C_6H_5SO_2NHOH$ and with Tollens' reagent.

The skeletal structure of this presumably dibromo aldehyde was determined in the following manner.

The dibromo aldehyde (500 mg.) was diluted with 10 cc. of dry ether, and the solution was added dropwise to a mixture of lithium-aluminum hydride (1 g.) (4) and lithium hydride (1 g.) in 10 cc. of anhydrous ether, maintained at its boiling point. The mixture was heated for a total of 2 hours. At the end of that time, ice-water was added to destroy the residual hydrides, and the solution was carefully neutralized with dilute hydrochloric acid. The ether layer was washed twice with a saturated solution of ammonium chloride, dried with sodium sulfate, and the ether was distilled. The residue was distilled in a Hickman flask and 80 mg. of colorless liquid was collected. The 3,5-dinitrobenzoate of this material melted at 62°, and it did not change the melting point of the 3,5-dinitrobenzoate prepared from a pure authentic sample of isoamyl alcohol.

(c) *Proof that the bromine atoms in the dimer are situated beta to each other.* To the dimer (500 mg.), dissolved in 10 cc. of benzene, was added the sodium derivative of phenylhydrazine (5) (1 g.). The mixture was heated to boiling for 10 hours. At the end of that time a good deal of sodium bromide had separated. The reaction mixture was then diluted with water, additional ether was added, the layers were separated, and the ether solution was washed repeatedly with water to remove the phenylhydrazine. The ether was then extracted with hydrochloric acid (2 *N*), the ether was rejected, the acid solution was made

alkaline and extracted with ether. The ether solution was removed, and the residue was distilled in a Hickman flask. The distillate was 1-phenyl-4-allylpyrazolidine (b.p. 130°/0.01 mm.; n_D^{20} 1.5860).

Anal. Calc'd for $C_{12}H_{16}N_2$: N, 14.9. Found: N, 14.8.

The picrate of the 1-phenyl-4-allylpyrazolidine was too soluble for crystallization. The picrolonate of this material, however, was readily obtained.

Anal. Calc'd for $C_{22}H_{24}N_6O_5$: N, 18.5. Found: N, 18.0.

The picrolonate crystallizes in yellow needles from ethyl alcohol. It melted at 186–187°, and its melting point was not depressed by admixture with a picrolonate of synthetic 1-phenyl-4-allylpyrazolidine prepared by a conventional method (5).

Synthesis of 4-bromomethyl-5-bromo-1-pentene. (a) *Preparation of 2-hydroxymethyl-4-penten-1-ol.* Lithium-aluminum hydride (5 g.) was suspended in 50 cc. of ether contained in a three-necked flask equipped with an efficient reflux condenser, a mechanical stirrer, and a dropping-funnel. To this mixture was added dropwise a solution of diethyl allylmalonate (b.p. 120°/18 mm.; n_D^{20} 1.4319) in 20 cc. of anhydrous ether. Upon completion of the addition, the mixture was refluxed for 30 minutes and cooled in an ice-salt mixture. Water was then added to destroy the excess of hydrides, and the solution was finally acidified with dilute sulfuric acid. Sufficient sodium sulfate to saturate the water solution was then added, and the whole was extracted with ether in a continuous extractor for 10 hours. The ether solution was then dried, and ether was removed by evaporation. The residue was distilled *in vacuo* (b.p. 136–139°/15 mm.; n_D^{20} 1.4747). The yield of 4-hydroxymethyl-4-penten-1-ol was 52% of the calculated amount.

Anal. Calc'd for $C_6H_{12}O_2$: C, 62.0; H, 10.3.
Found: C, 62.2; H, 10.2.

The bis-3,5-dinitrobenzoate of the 4-hydroxymethyl-4-penten-1-ol crystallizes in white needles from ethyl acetate and melts sharply at 145–146°.

Anal. Calc'd for $C_{20}H_{16}N_4O_{12}$: N, 11.1. Found: N, 10.6.

(b) *Preparation of 4-bromomethyl-5-bromo-1-pentene.* To 2-hydroxymethyl-4-penten-1-ol (6 g.) dissolved in 10 cc. of dry benzene was added dry pyridine (0.5 cc.), and the whole was cooled to 0°. To this mixture was added a solution of phosphorus tribromide (12 g.) in 10 cc. of dry benzene. Upon completion of the addition, the mixture was kept for 10 hours at room temperature, and then heated for 8 hours at 80°. Water was then added to destroy the excess of phosphorus tribromide, and the whole was extracted with ether. The ether extract was washed successively with a water solution of sodium bicarbonate, dilute hydrochloric acid, and water. The ether-benzene mixture was dried over sodium sulfate, and the solvents were removed by distillation. The residue was distilled through a Vigreux column and the following fractions were collected: Fraction 1, b.p. 93–95°/15 mm., n_D^{20} 1.5204; Fraction 2, b.p. 138–141°/15 mm., n_D^{20} 1.5454.

Fraction 1 is undoubtedly 4-bromomethyl-5-bromo-1-pentene and corresponds in physical constants to the dimer prepared by treating allyl bromide with diacetyl peroxide. Further to confirm the identity of these materials, the material of Fraction 1 was heated with sodium phenylhydrazine to give 1-phenyl-4-allylpyrazolidine. The picrolonate of this pyrazolidine melted at 185–187° and did not depress the melting point of the picrolonate of the 1-phenyl-4-allylpyrazolidine, prepared from the dimer of allylbromide. The identity of these materials is thus established. Furthermore, the dimer of allyl bromide formed in the decomposition of diacetyl peroxide in that solvent, is definitely established as 4-bromomethyl-5-bromo-1-pentene.

Fraction 2 (b.p. 138–141°/15 mm.; n_D^{20} 1.5454) is probably formed by the addition of hydrogen bromide to 4-bromomethyl-5-bromo-1-pentene, the product is therefore 1,4-dibromo-2-bromomethylpentane.

Anal. Calc'd for $C_6H_{11}Br_3$: Br, 74.3; mol. wt., 323.
Found: Br, 74.0; mol. wt., 309.

SUMMARY

1. The decomposition of diacetyl peroxide in allyl bromide was shown to give the following products: butene-1, methyl bromide, 1,3-dibromopropane, 4-bromomethyl-5-bromo-1-pentene, possibly 1,5-bromo-2-bromomethylpentane, and a blackresidue resembling pitch.

2. A mechanism to account for the reaction products is suggested.

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[Contribution from the George Herbert Jones Laboratory of the University of Chicago]

REACTIONS OF ATOMS AND FREE RADICALS IN SOLUTION. XVIII. DECOMPOSITION OF DIACETYL PEROXIDE IN *vic*-GLYCOLS

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It has been postulated (1) that lead tetraacetate decomposes, when heated in solvents, to give lead diacetate and diacetyl peroxide or lead acetate and free acetoxy (and/or free methyl) radicals:

1. $Pb(OCOCH_3)_4 \rightarrow Pb(OCOCH_3)_2 + 2CH_3COO\cdot$

   $CH_3COO\cdot \rightarrow CH_3\cdot + CO_2$

2. $Pb(OCOCH_3)_4 \rightarrow Pb(OCOCH_3)_2 + (CH_3COO)_2$

Since this hypothesis postulates either the formation of diacetyl peroxide or fragments presumably similar to those assumed in the decomposition of diacetyl peroxide (2), the decomposition of lead tetraacetate and of diacetyl peroxide in acetic acid and diisopropyl ether was investigated (3). Because the reaction products were different in the two cases, it was concluded that although some free radicals (methyl and acetoxy) are formed in the decomposition of lead tetraacetate in these solvents, the reaction mechanism in the case of lead tetraacetate is not dependent upon either of the mechanisms (1 and 2) postulated above.

Further to confirm that when heated in solvents lead tetraacetate does not decompose into fragments similar to those formed from diacetyl peroxide, the decomposition of diacetyl peroxide in *vic*-glycols (2,3-butanediol and hydrobenzoin) was investigated.

RESULTS

The results obtained by the decomposition of diacetyl peroxide in 2,3-butanediol and hydrobenzoin are given in Tables I and II. Because of the experimental difficulties involved in the separation of acetoin (Table I) and in separating benzil, benzoin, and hydrobenzoin (Table II), three compounds whose physical properties are quite similar (solubility in solvents and melting points), our balance sheets for the entire reaction are not as adequate as in other reactions involving the decomposition of diacetyl peroxide. Nevertheless, the results are quite unambiguous. The *vic*-glycols when treated with diacetyl peroxide give the corresponding hydroxy ketones and diketones. The aldehydes or ketones, which are formed in such excellent yields when lead tetraacetate is used, are formed in insignificant quantities when diacetyl peroxide is used.

The 2,3-butanediol used in experiment 2 (Table I) had 4.6% of the hydroxyl hydrogen atoms replaced by deuterium. Yet, the methane produced in the reaction contained less than 0.01% of deuterium.

When pinacol, dissolved in acetic acid, is treated with acetyl peroxide, it is recovered unchanged, while the acetic acid is converted to succinic acid.

TABLE I

THE DECOMPOSITION OF DIACETYL PEROXIDE IN 2,3-BUTANEDIOL

REACTANTS	MOLES	MOLES
2,3-Butanediol	6.4	7.3
Diacetyl peroxide	1.0	1.0
PRODUCTS	**MOLES/MOLE ACETYL PEROXIDE**	**MOLES/MOLE ACETYL PEROXIDE**
Carbon dioxide	1.0	1.3
Carbon monoxide	0.0	0.0
Methane (contains small percentage of ethane)	0.97	1.3
Methyl acetate	0.0	0.0
Acetic acid	0.74	0.77
Acetoin	0.39	0.26
Biacetyl	0.18	0.13
Acetaldehyde	0.01_3	0.00_5

TABLE II

THE DECOMPOSITION OF DIACETYL PEROXIDE IN HYDROBENZOIN

REACTANTS	MOLES
Diacetyl peroxide	1.0
Hydrobenzoin	1.08
t-Butyl alcohol	6.0
PRODUCTS	**MOLES/MOLE ACETYL PEROXIDE**
Carbon dioxide	1.04
Carbon monoxide	0.0
Methane	0.71
Ethane	0.12
Acetic acid	0.74
Methyl acetate	0.06
Benzoin	0.14
Benzil	0.18
Benzaldehyde	trace
Recovered hydrobenzoin	0.58

DISCUSSION

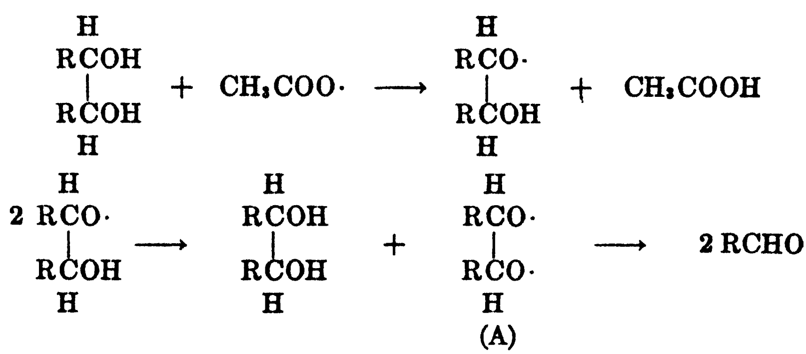
The fact that diacetyl peroxide when heated in *vic*-glycols does not break the carbon-to-carbon bond of the glycols, but forms the corresponding keto alcohols and diketones, invalidates, in our estimation, the hypothesis that in the oxidation of *vic*-glycols lead tetraacetate functions by virtue of a *primary* breakdown into lead acetate and free acetoxy radicals, or lead acetate and acetyl peroxide (1).

There is another fundamental difference between lead tetraacetate and acetyl peroxide insofar as the reactions with glycols and alcohols are concerned. The

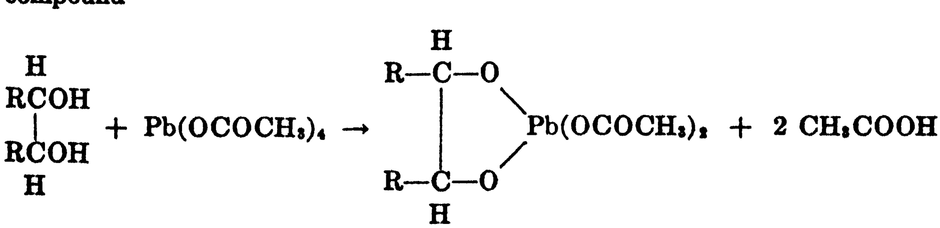
difference is in the point of the initial attack of these reagents. Acetyl peroxide attacks the hydrogen atom attached to the carbon atom holding the hydroxyl group, whereas lead tetraacetate attacks the hydroxyl hydrogen atoms. These facts help to explain why acetyl peroxide attacks acetic acid solutions of *vic*-glycols such as hydrobenzoin or 3,4-butanediol more readily than glycols of the type of pinacol (which it does not attack in acetic acid solution), whereas lead tetraacetate attacks all of these *vic*-glycols with equal ease.

Furthermore, there is no evidence that the free radicals, formed by the decomposition of diacetyl peroxide in alcohols, ever attack the hydrogen atom of the hydroxyl group. Thus, acetyl peroxide attacks isopropyl alcohol with greater ease than *t*-butyl alcohol, indicating an attack on different atoms in the two molecules. Furthermore, deuterium tracer experiments have shown that deuterium atoms attached to the oxygen atoms in 2,3-butanediol are not attacked by the free radicals formed by the decomposition of diacetyl peroxide. Similar results were obtained with deuterium tracer experiments with *t*-butyl alcohol and isopropyl alcohol in which the deuterium was attached to the oxygen atom. The methane formed in all cases contained less than 0.01% of deuterium. On the other hand, the methane formed by decomposition of diacetyl peroxide in isopropanol in which some of the hydrogen atoms on the carbon atoms carrying the hydroxyl groups were replaced by deuterium, gave a mixture of methane and deuteromethane containing approximately the statistically calculated amount of deuterium (4).

Our evidence is thus contrary to the hypothesis of Waters (1) that free radicals are intermediates in the oxidation of *vic*-glycols.



For the reasons here cited, as well as other reasons (5), we favor the hypothesis (6) that oxidation of *vic*-glycols proceeds through the formation of a cyclic lead compound



which breaks down to give lead acetate and two molecules of the aldehyde. It is purely a matter of taste whether one wishes to postulate the transient existence during this breakdown of a biradical (A), which at once decomposes into two molecules of aldehyde or ketone.

The mechanism of the decomposition of diacetyl peroxide in *vic*-glycols may be postulated in a manner similar to that of the induced decomposition of benzoyl peroxide in alcohols (7).

1. $CH_3CO_2O_2CCH_3 \rightarrow CH_3CO_2\cdot\ CH_3\cdot + CO_2$
2. $CH_3CO_2\cdot \rightarrow CH_3\cdot + CO_2$
3. $2CH_3CO_2\cdot \rightarrow CH_3CO_2CH_3 + CO_2$
4. $CH_3\cdot + CH_3CO_2O_2CCH_3 \rightarrow CH_3CO_2CH_3 + CH_3CO_2\cdot$
5. $CH_3\cdot + CH_3CO_2O_2CCH_3 \rightarrow C_2H_6 + CH_3CO_2\cdot + CO_2$
6. $CH_3\cdot + RCH(OH)CH(OH)R \rightarrow CH_4 + \cdot C(OH)RCH(OH)R$
7. $\cdot C(OH)RCH(OH)R + CH_3CO_2O_2CCH_3 \rightarrow RCH(OH)C(OH)(OCOCH_3)R + CH_3\cdot + CO_2$
8. $RCH(OH)C(OH)(OCOCH_3)R \rightarrow RCH(OH)COR + CH_3CO_2H$
9. $CH_3\cdot + RCH(OH)COR \rightarrow CH_4 + \cdot C(OH)(COR)R$
10. $\cdot C(OH)(COR)R + CH_3CO_2O_2CCH_3 \rightarrow RCOC(OH)(OCOCH_3)R + CH_3\cdot + CO_2$
11. $RCOC(OH)(OCOCH_3)R \rightarrow RCOCOR + CH_3CO_2H$

Reactions 3, 4, and 5 are side reactions. Reactions 6 and 7 and corresponding reactions 9 and 10 constitute the main reaction chain.

It is noteworthy, that in all induced decompositions of diacetyl peroxide about equimolar quantities of acetic acid and methane are formed; while in the non-induced decomposition reactions of diacetyl peroxide small amounts, if any, of acetic acid are formed.[1]

EXPERIMENTAL

Decomposition of acetyl peroxide in 2,3-butanediol. A solution of acetyl peroxide (36.5 g., 0.31 mole) in 2,3-butanediol[2] (180 g., 2 moles, n_D^{20} 1.4363) was dropped into a flask held at 95°. A gas-collector train of the type previously described (8) was used to collect the carbon dioxide (13.5 g., 0.31 mole) and the methane (7.5 l., 0.3 mole). The reaction mixture was distilled and separated into the following fractions: 1. a low-boiling fraction containing biacetyl, acetic acid, and traces of acetaldehyde; 2. a medium-boiling fraction containing acetic acid and acetoin; 3. the bulk of the 2,3-butanediol containing some acetoin. The

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[1] Except with molecules containing very active hydrogen atoms, such as aldehydes, in which the hydrogen atoms can be removed by free acetoxy radicals.

[2] The 2,3-butanediol (90% *meso*, 10% *dextro*) was obtained through the kindness and generosity of the Northern Regional Research Laboratory of the Department of Agriculture at Peoria, Illinois.

acetic acid was determined by titration of an aliquot with 0.1 N sodium hydroxide. The acetaldehyde was determined quantitatively by precipitation as the methone derivative (9) which melted at 139.5–140.5°. The melting point of the methone derivative of acetaldehyde (9) given in the literature is 135–140°.

The acetoin (Fraction 2) and the biacetyl (Fraction 1) were determined quantitatively by precipitation with 2,4-dinitrophenylhydrazine (10). The results thus obtained were in close agreement with those calculated from the refractive indices of the various fractions. The biacetyl and acetoin were further identified by reaction with phenylhydrazine. Biacetyl formed a bis-phenylhydrazone which melted at 244–245°. Acetoin formed a phenylosazone which melted at 247–248°. The two compounds, however, are identical, and they did not depress the melting point of each other. The recorded melting point of the bis-phenylhydrazone of biacetyl is 243°.

Decomposition of diacetyl peroxide in 2,3-butanediol containing deuterium. The method employed for the decomposition of the diacetyl peroxide was the same as previously described, except that the 2,3-butanediol contained 4.6% deuterium in place of hydrogen atoms in the hydroxyl groups. The deutero-2,3-butanediol was prepared by allowing 2,3-butanediol to equilibrate with heavy water for 24 hours. The glycol was then dried with calcium sulfate and distilled at reduced pressure. The partially deuterated 2,3-butanediol (n_D^{20} 1.4351) boiled at 91–92° at 19 mm. The amount of deuterium was determined by allowing the glycol to react with methylmagnesium iodide in butyl ether. The methane produced was burned over a hot platinum wire, and the density of the water was determined by the flotation temperature of a calibrated quartz float (4). The amount of deuterium in the methane from the acetyl peroxide decomposition was determined in a similar fashion. The amount of deuterium in the methane formed by the decomposition of diacetyl peroxide was less than 0.01%. The reaction mixture was distilled as previously described. The amounts of acetoin and biacetyl formed in the reaction were determined, however, by the empirical method of Langlykke and Peterson (11). The agreement of the two experiments was very good (see Table I).

Decomposition of diacetyl peroxide in hydrobenzoin. The diacetyl peroxide and the hydrobenzoin were dissolved in t-butyl alcohol; otherwise the procedure was the same as described previously for the decomposition of the diacetyl peroxide in 2,3-butanediol.

The reaction mixture was subjected to fractional crystallization first from the solvent and then from ethyl ether and from alcohol. The course of the fractionation was followed by noting changes in the melting points of the fractions when these were mixed with authentic samples of benzoin, benzil, and hydrobenzoin. As a check on the separation of the mixtures the precipitation of 2,4-dinitrophenylhydrazones (10) was undertaken. The results of these experiments were in fair agreement with those obtained by the fractional crystallizations. Benzil was identified by the melting point 125–126° of 2,3-diphenylquinoxaline prepared from it and o-phenylenediamine. The melting point given in the literature is 126.2°. The 2,4-dinitrophenylhydrazone of benzoin melted at 235–236°, and it did not depress the melting point of an authentic sample. The benzaldehyde was identified by conversion to its 2,4-dinitrophenylhydrazone. The material melted at 235–237°, and it did not depress the melting point of an authentic sample of the 2,4-dinitrophenylhydrazone of benzaldehyde

SUMMARY

1. The reaction of acetyl peroxide with 2,3-butanediol gave carbon dioxide, methane, acetic acid, acetoin, biacetyl, and only a trace of acetaldehyde.

2. Deuterium tracer experiments have demonstrated that the hydrogen atom attached to the oxygen atom is not attacked by the free radical fragments formed in the decomposition of diacetyl peroxide.

3. The reaction of acetyl peroxide with hydrobenzoin in t-butyl alcohol so-

lution gave carbon dioxide, methane, methyl acetate, acetic acid, benzoin, benzil, and only a trace of benzaldehyde.

4. The bearing of these results on the mechanism of the action of lead tetraacetate on *vic*-glycols is discussed.

5. A mechanism for the decomposition of acetyl peroxide in glycols is proposed.

CHICAGO 37, ILL.

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[CONTRIBUTION FROM THE PURDUE RESEARCH FOUNDATION AND THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

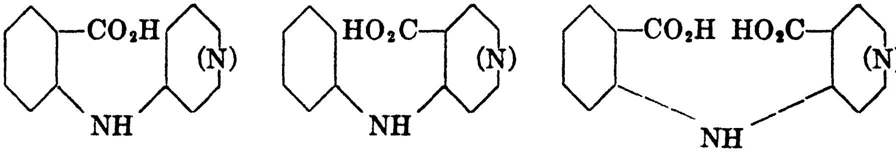
DERIVATIVES OF THE PYRIDOQUINOLINES[1]

G. BRYANT BACHMAN AND ROBERT S. BARKER[2]

Received September 1, 1948

As part of the antimalarial program pursued in this laboratory it was decided to attempt the preparation of compounds like Atabrine (quinacrine) but with one of the benzene rings replaced by a pyridine ring. There is good evidence that an electron withdrawing group in the 2-position of the Atabrine nucleus can replace the usual 3-chloro group without marked diminution in activity. Thus, the 2-nitro and the pyrido(3,2-a) derivatives of 7-methoxy-9-substituted-amino-acridines are reported active (1, 2).

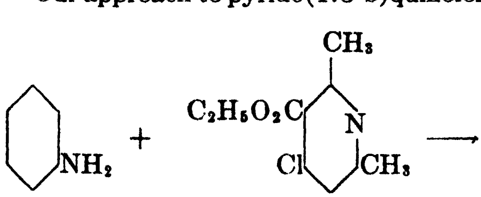
A reasonable approach to pyridoquinolines would appear to be *via* ring closure reactions on acids of the following types.



Ia Ib Ic

The resulting pyridoquinolones (using H_2SO_4) or chloropyridoquinolines (using $POCl_3$) could then be converted into the desired amino derivatives by processes which are well known in the acridine series. Actually it was found that acids of type Ia will decarboxylate before they will dehydrate to pyridoquinolones, acids of type Ib will undergo ring closure only under certain unfavorable circumstances, and acids of type Ic (only one of which was tested) give no detectable amounts of pyridoquinolones when heated in the form of their calcium salt to 400°. These observations correspond for the most part with previously reported results. Kermack (3) and Petrow (4) were unable to cyclize various N-pyridyl-anthranilic acids (type Ia) and N-anthranylpyridines (type Ib).

Our approach to pyrido(4.3-b)quinolones is illustrated below.



II

[1] From the Ph.D. thesis of R. S. Barker, Purdue University, June 1948. Read before the Organic Division at the St. Louis meeting of the American Chemical Society, September 1948.

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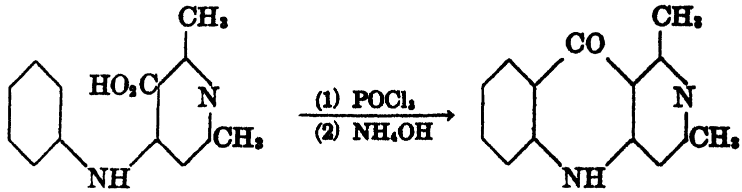
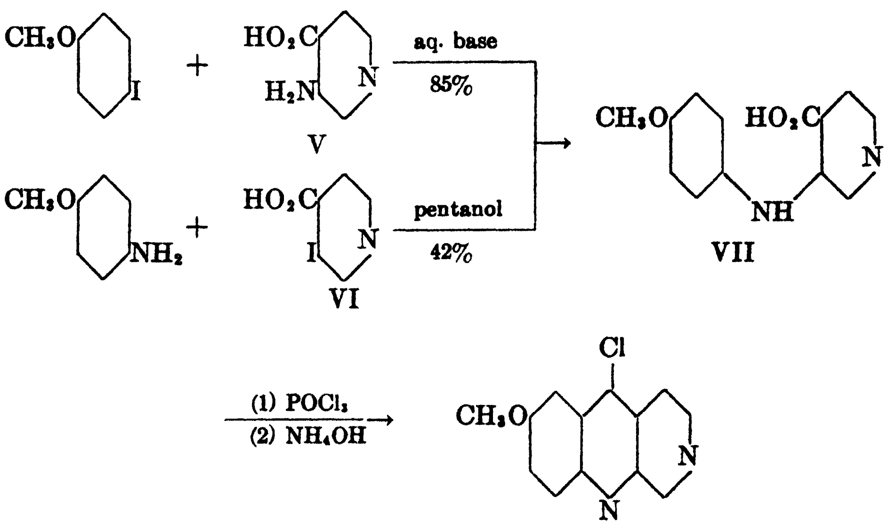


III IV

The reactions proceeded in excellent yields, but all attempts to convert IV to a 9-chloropyridoquinoline with $POCl_3$, PCl_5, etc. were unsuccessful. Furthermore, if the methyl substituents of II were eliminated, not even a pyridoquinolone could be obtained. Ring closure is apparently dependent on the presence of activating groups such as methyl. Attempts to prepare 9-aminopyridoquinolines directly, by heating IV with urea, ammonium formate, or 3-diethylaminopropylamine, were completely unsuccessful. Also treatment of IV with P_2S_5 did not yield the 9-thiol (5).

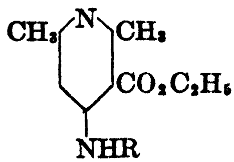
The pyrido(3.4-b)quinolones were approached as shown in formulas V–VIII

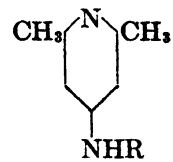


V VI VII VIII

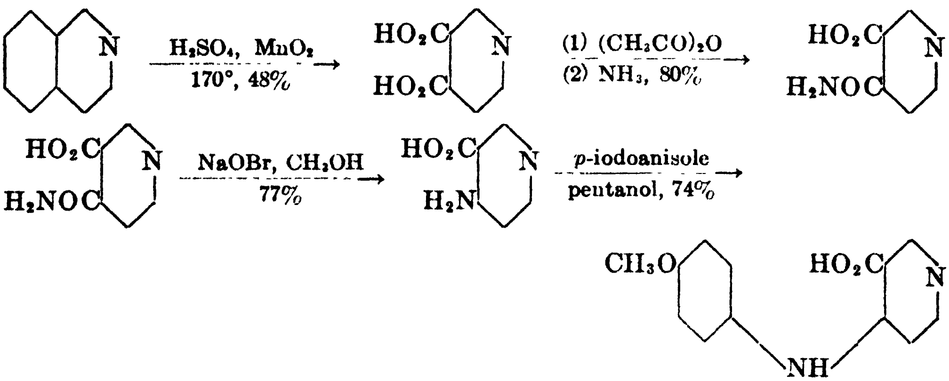
Treatment of VII with $POCl_3$ did not give the desired pyridoquinolone or the chloropyridoquinoline (VIII).

Synthesis of intermediates. Ethyl 4-chloro-2,6-dimethylnicotinate (II) was prepared from ethyl 3-aminocrotonate through treatment with $POCl_3$, in twice the yields obtained previously (6), by reaction at 100° in the absence of solvents. Its condensation with amines (aniline, *p*-anisidine, 2-naphthylamine, 6-methoxy-8-aminoquinoline, and 4-diethylamino-1-methylbutylamine) gave not only products like III but also the corresponding ester IX and the decarboxylated pyridine X. Appreciable amounts of X were also isolated when III was treated with $POCl_3$.


IX

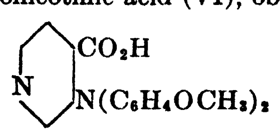

X

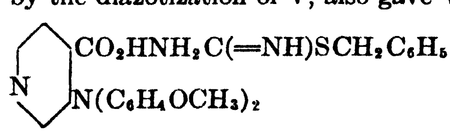
The preparation of unmethylated III was laborious. Isoquinoline was sulfonated and then oxidized by MnO_2 to cinchomeronic acid. This was converted to 4-aminonicotinic acid by improved procedures and then condensed with *p*-iodoanisole to give XI.

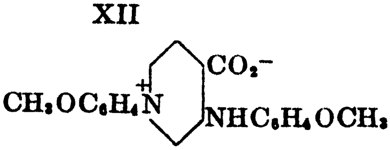

XI

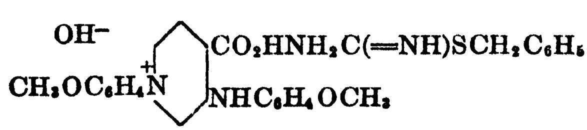
Numerous attempts to convert XI to the desired chloropyridoquinoline or even to the pyridoquinolone were unsuccessful. Products of unknown structure and tars were obtained.

3-Aminoisonicotinic acid (V) was prepared from cinchomeronimide *via* the Hofmann degradation with hypobromite. Its condensation with *p*-iodoanisole gave VII under the indicated conditions, but in refluxing hexanol an entirely different product (XII) was obtained. Condensation of *p*-anisidine with 3-iodoisonicotinic acid (VI), obtained by the diazotization of V, also gave VII.


XII


XIII


XIV


XV

An analysis of the S-benzylthiouronium salt (XIII) helped in determining the structure of XII. The percentages of carbon, hydrogen, and sulfur showed that XIII and hence XII had been formed, rather than XV and hence XIV.

Pharmacological testing. The hydrochlorides of IV were found inactive against *Streptococcus hemolyticus*, influenza virus, tetanus, rabic virus, and trypanosomes. The hydrochloride of IX, when R was 6-methoxy-8-aminoquinolinyl, showed no activity as a germicide or bacteriostatic agent. It was slightly active as an amebicide. The hydrochlorides of X, when R was the 4-diethylamino-1-methylbutylamine side chain, and of IV and IX showed no antimalarial activity.

Acknowledgment. The authors wish to express their appreciation to Eli Lilly and Company for financial support in the form of a fellowship and for pharmacological testing.

EXPERIMENTAL

Ethyl 4-chloro-2,6-dimethylnicotinate (II). cf. (6). Ethyl 3-aminocrotonate (6, 7), 785 g., was slowly added to stirred phosphorus oxychloride, 1890 g., at 100°. The mixture was stirred until the evolution of hydrogen chloride became negligible, the excess phosphorus oxychloride was removed under a vacuum and the mixture was carefully poured into 6 kg. of cracked ice. After neutralization with alkali below 25°, the product was extracted with benzene, dried with sodium carbonate, treated with Norit, filtered, and distilled to yield 393 g. (70%) of product, b.p. 97–105° (2 mm.), n_D^{27} 1.5032.

4-Substituted-2,6-dimethylnicotinic acids (III). These were all prepared essentially in the same way. *p*-Anisidine, 12 g., and ethyl 4-chloro-2,6-dimethylnicotinate, 10 g., were cautiously warmed to 150° and the reaction allowed to proceed spontaneously. The temperature rose to 205°, where it was held for 4 minutes. The cooled gummy residue was dissolved in a mixture of benzene and dilute alkali, the aqueous phase treated with Norit, filtered and neutralized with dilute hydrochloric acid. When crystallized from 50% methanol or 5% acetic acid, 4-(*p*-methoxyphenylamino)-2,6-dimethylnicotinic acid, 7.2 g., m.p. 271–272°, was obtained.

Anal. Calc'd for $C_{15}H_{16}N_2O_3$: N, 10.28. Found: N, 10.08, 10.20.

The benzene layer was extracted with water, dried and distilled. The residue was crystallized from isopropyl ether to yield a small amount of ethyl 4-(*p*-methoxyphenylamino)-2,6-dimethylnicotinate (IX), m.p. 92–93°. This compound was also prepared by heating equal quantities of the chloro ester and *p*-anisidine on a steam-bath for several hours. The residue was made alkaline, extracted with a large quantity of ether, dried, and the ether was distilled. The residue was crystallized from isopropyl ether a number of times.

Anal. Calc'd for $C_{17}H_{20}N_2O_3$: N, 9.34. Found: N, 9.35, 9.49.

The 4-phenylamino analog of III was crystallized from cold water, m.p. 244–245° (6); the hydrochloride from chloroform-ether, m.p. 167–168°.

The 4-(2'-naphthylamino) analog of III was crystallized from aqueous ethanol, m.p. 262–263°.

Anal. Calc'd for $C_{18}H_{16}N_2O_2$: N, 9.59. Found: N, 9.65, 9.57.

Pyrido(4.3-b)quinolones (IV). These were all prepared in the same manner. 4-(*p*-Methoxyphenylamino)-2,6-dimethylnicotinic acid, 22.5 g., was gently refluxed 3–4 hours with phosphorus oxychloride, 100 g. About one-third of the solvent was removed under vacuum and the residual mixture was poured on ice. The black solution was neutralized with aqueous potassium carbonate, the precipitate washed with ether and crystallized from ethanol to yield yellow crystals of 1,3-dimethyl-8-methoxypyrido(4.3-b)quinolone, m.p. 298–299°. The hydrochloride, 14.7 g. (69.9%), from ethanol, melted at 319–320° (d.) (copper block, 60 seconds).

Anal. Calc'd for $C_{15}H_{14}N_2O_2(HCl)$: N, 9.64; Cl, 12.22.
Found: N, 9.73, 9.66; Cl, 12.22, 12.09.

The alkaline carbonate filtrate from the initial reaction was extracted with ether and all the ether washings were combined and dried with sodium hydroxide, filtered, and saturated with hydrogen chloride, to yield the hydrochloride of 4-(*p*-methoxyphenylamino)-2,6-dimethylpyridine (X), m.p. 229–230°, (from ethanol-ether).

Anal. Calc'd for $C_{14}H_{16}N_2O(HCl)$: N, 10.59. Found: N, 10.42, 10.48.

A similar reaction with 4-phenylamino-2,6-dimethylnicotinic acid yielded 1,3-dimethylpyrido(4.3-b)quinolone, m.p. 319–320° (d.), (from ethanol); hydrochloride (from ethanol), 376–378° (d.).

Anal. Calc'd for $C_{14}H_{12}N_2O(HCl)$: N, 10.72; Cl, 13.59.
Found: N, 10.62, 10.70; Cl, 13.59, 13.52.

4-(2′-Naphthylamino)-2,6-dimethylnicotinic acid yielded pale-yellow 1,3-dimethylpyrido(4.3-b)benzo(f)quinolone, m.p. 280–282° (d.), (from pyridine or acetic acid).

Anal. Calc'd for $C_{18}H_{14}N_2O$: N, 10.21. Found: N, 10.00, 9.92.

Ethyl 2,6-dimethyl-4-(6′-methoxy-8′-quinolinylamino)nicotinate. Ethyl 4-chloro-2,6-dimethylnicotinate, 48 g., was added to butanol (300 ml.) containing 10 g. of hydrogen chloride, and 45 g. of 8-amino-6-methoxyquinoline. After refluxing for twenty-four hours the butanol was removed under vacuum, the residue taken up in water and neutralized with alkali. The precipitate was washed with a small amount of ether and crystallized from di-*n*-butyl ether (Norit) to yield 41 g. (42.5%) of product, m.p. 149–150°. The hydrochloride (from butanol-ether, or 2-propanol) melted at 247–248°. The original ether washings were shaken with Norit and powdered sodium hydroxide, filtered, and cooled overnight to yield 7.5 g. (7.9%) more product.

Anal. Calc'd for $C_{20}H_{21}N_3O_3(HCl)$: N, 10.83. Found: N, 10.76, 10.81.

2,6-Dimethyl-4-(5′-diethylamino-2′-pentylamino)pyridine. Ethyl 4-chloro-2,6-dimethylnicotinate, 30 g., 4-diethylamino-1-methylbutylamine, 35 g., sodium iodide, 0.2 g., and copper powder, 0.1 g., were held at 205° for three hours. The reaction mixture was cooled and shaken with a mixture of ether and 5 *N* sodium hydroxide. The ether layer was dried over potassium hydroxide and distilled to yield 19 g. of the 4-substituted pyridine, b.p. 163–165° (2 mm.). On redistillation the product boiled at 130–135° (0.5–1 mm.). The chloroplatinate derivative, red buttons from 50% ethanol, melted at 229–230°.

Anal. Calc'd for $C_{16}H_{29}N_3$: C, 72.90; H, 11.12; N, 15.98.
Found: C, 72.77, 72.70; H, 10.95, 11.02; N, 16.04, 16.15.

Cinchomeronic acid. The procedure is essentially that of van de Kamp and Sletzinger (8), for the preparation of quinolinic acid from quinoline. The product, however, was isolated in a different manner. The amber-colored solution obtained from the oxidation of sulfonated isoquinoline, instead of being treated with a cupric salt, was neutralized with sodium carbonate to *p*H 1 and the precipitated cinchomeronic acid filtered off after fifteen hours. The yields were 48–55%.

4-Cinchomeronic acid amide (9). Cinchomeronic anhydride (10) (prepared by refluxing 100 g. of the acid with 400 g. of acetic anhydride for 30 minutes, filtering, and removing the acetic acid and anhydride under vacuum, then distilling the product under vacuum) was taken up in 2 l. of benzene and 35 g. of dry ammonia bubbled into the refluxing and stirred solution. The mixture was cooled, hot water added and the aqueous phase was removed and saturated with sulfur dioxide at 25° to precipitate the acid amide. The filtrate yielded more product (total 65 g. or 80%) on standing overnight in an ice-box. The product was crystallized from water, washed with acetone and dried, m.p. 170–171°.

4-Aminonicotinic acid (9). Thirty-six grams of 4-cinchomeronic acid amide was dissolved with vigorous stirring and cooling in 325 ml. of 7% sodium methoxide in methanol. The solution was chilled to 0°, 32 g. of bromine slowly added, stirred for one hour at 0°, then refluxed for 20 minutes. The milky mixture was distilled under vacuum to remove the methanol, the residue was dissolved in hot water containing 40 g. of sodium hydroxide and the mixture was refluxed for several hours. It was concentrated to about 250 ml., 50 ml. of

5 N hydrochloric acid was added and the pH adjusted to 5–6 with acetic acid. The crystalline product which precipitated, 21.5 g. (77.5%), was crystallized from hot water (Norit), m.p. 338–341°.

Cinchomeronimide (II). Cinchomeronic anhydride, from 250 g. of the acid, was stirred with 240 g. of acetamide at 100° for 60 hours, the mixture cooled and triturated with cold water, then filtered. Upon crystallization from acetic acid, 189 g. (91%) of the imide, m.p. 226–227° [reported 229–230° (11)], was obtained.

3-Aminoisonicotinic acid (V). This compound was prepared according to the method of Gabriel and Coleman (12) from cinchomeronimide by the Hofmann hypobromite reaction. The product melted at 319–320° (reported 307–310°) after a number of crystallizations from hot water.

4-(p-Methoxyphenylamino)nicotinic acid (XI). A mixture of 29 g. of 4-aminonicotinic acid, 55 g. of p-iodoanisole, 30 g. of potassium carbonate, 125 ml. of n-pentanol, and 0.2 g. of a copper-copper oxide mixture (1:1) was refluxed (nitrogen atmosphere and stirring) for seventy-two hours, cooled, diluted with ether, and filtered. The precipitate was dissolved in hot dilute alkali, treated with Norit, then fractionally precipitated by the addition of small amounts of dilute hydrochloric acid. The solid precipitate, 38 g. (74%) was crystallized from hot water to yield white needles, m.p. 290–291°. It was easily soluble in methanol, less soluble in ethanol and difficultly soluble in propanol. It was soluble to the extent of 0.3–0.4% in hot water and was practically insoluble in cold water.

Anal. Calc'd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47.
Found: C, 63.52, 63.63; H, 5.18, 5.14; N, 11.40, 11.49.

An S-benzylthiouronium salt was prepared according to the method of Donleavy (13). No reproducibly sharp melting point could be obtained. The range was 160–175°, depending on the amount of sample and the rapidity of heating.

Anal. Calc'd for $C_{21}H_{22}N_4O_3S$: C, 61.46; H, 5.40; S, 7.82.
Found: C, 61.55, 61.51; H, 5.40, 5.45; S, 8.04, 7.92.

3-(N,N-Di-p-methoxyphenylamino)isonicotinic acid (XII). A mixture of 38.5 g. of 3-aminoisonicotinic acid, 68 g. of p-iodoanisole, 200 ml. of hexanol, 48 g. of potassium carbonate, and 0.5 g. of a copper-copper oxide (1:1) mixture was refluxed for seventy-two hours (nitrogen atmosphere and stirring), then steam distilled. The residue was dissolved in alkali, treated with Norit, filtered, and the mixture adjusted to exactly 0.1 N with hydrochloric acid. The red mixture was heated to 95° (more hydrochloric acid being added to adjust the pH) and allowed to cool. The orange product which separated was filtered off and crystallized from ethanol, m.p. 239–240°. The aqueous mother liquors on neutralization with alkali precipitated the starting amino acid. The orange product (XII) was red in acid solutions up to pH 4, going slowly to yellow at pH 7, and becoming practically colorless at higher pH's. It was insoluble in 0.1 N acids but soluble in stronger acids.

Anal. Calc'd for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.14; N, 7.99.
Found: C, 68.37, 68.43; H, 4.98, 5.08; N, 7.98, 8.05.

An S-benzylthiouronium derivative was prepared according to the method of Donleavy (13). It did not have a satisfactory melting point.

Anal. Calc'd for $C_{28}H_{28}N_4O_4S$: C, 65.10; H, 5.46; S, 6.20.
Found: C, 64.82, 64.95; H, 5.44, 5.43; S, 6.26, 6.40.

3-Iodoisonicotinic acid (VI). 3-Aminoisonicotinic acid, 13 g., in water, 200 ml., and concentrated sulfuric acid, 25 g., were diazotized at 0° with potassium nitrite, 8.6 g., in water, 50 ml. After the solution showed no reaction to starch iodide paper (urea was sometimes added if too much nitrite was present) it was poured into 100 ml. of water containing 20 g. of sodium iodide, allowed to stand overnight and then held at 50–60° until the evolution of nitrogen had ceased. (In those reactions where no nitrogen was evolved during the first few minutes of heating, the heating step was omitted.) The mixture was finally chilled, and the black precipitate crystallized from acetic acid to yield 18 g. (76%) of yellowish 3-iodoisonicotinic acid, m.p. 240–241°. The aqueous filtrate was saturated with sulfur dioxide and allowed to remain overnight at 0° to recover further amounts of product. All of the

product was dissolved in a minimal amount of hot pyridine, about 125 ml. of ethanol added, the solution treated with Norit, cooled, and saturated with sulfur dioxide at about 15°. A small amount of the precipitated product was crystallized from ethanol (Norit) to yield white granular crystals, m.p. 244–244.5°.

Anal. Calc'd for $C_6H_4INO_2$: C, 28.93; H, 1.61.

Found: C, 29.07, 29.13; H, 1.83, 1.88.

3-(p-Methoxyphenylamino)isonicotinic acid (VII). Method A. 3-Iodoisonicotinic acid, 2.5 g., *p*-anisidine, 3.0 g., potassium carbonate, 2.8 g., pentanol, 7 ml., and copper-copper oxide, 0.1 g., were refluxed (nitrogen atmosphere and stirring) for ten hours. The black mixture was steam distilled, treated with Norit, and the product fractionally precipitated with 5 *N* hydrochloric acid. The desired golden-yellow product precipitated first, 1.0 g. (42%) m.p. 310–312° (d.) (from pyridine-water or acetic acid). The product was titrated at 70° (phenolphthalein) with hydrochloric acid: neutral equivalent 241 (theory, 244).

Method B. 3-Aminoisonicotinic acid, 14 g., *p*-iodoanisole, 24 g., potassium carbonate, 28 g., Aerosol O.T., 1 g., copper-copper oxide, 0.5 g., propanol, 10 ml., and water, 100 ml., were refluxed for seventy hours, the reaction mixture was steam distilled, and the aqueous residue was treated as described in Method A. Nineteen grams (82%) of product was obtained.

Anal. Calc'd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.46.

Found: C, 63.89, 63.83; H, 4.92, 4.98; N, 11.43, 11.50.

3-(Phenylamino)isonicotinic acid. Fourteen grams of 3-aminoisonicotinic acid and 22 g. of iodobenzene were treated as in Method B (above) to obtain a 60% yield of yellow crystals, m.p. 305–306° (d.).

Anal. Calc'd for $C_{12}H_{12}N_2O_2$: N, 12.98. Found: N, 12.79, 13.06, 12.73.

3-(2'-Carboxy-4'-methoxyphenylamino)isonicotinic acid (Ic). 3-Iodoisonicotinic acid, 12.5 g., 5-methoxyanthranilic acid, 10.2 g., copper-copper oxide, 0.1 g., potassium carbonate, 28 g., and water, 100 ml., were treated as in Method B (reflux for 10 hours). The product was crystallized from pyridine-water or acetic acid to yield 12.3 g. (85%) of yellow crystals, m.p. 317–319° (d.).

Anal. Calc'd for $C_{14}H_{12}N_2O_5$: N, 9.41. Found: N, 9.46, 9.46.

The calcium salt of Ic (4 g.) was mixed with fine sand and held at 400° for 30 minutes under 2 mm. pressure. No pyridoquinolone sublimed. The residue was extracted with hot ethanol and the ethanol evaporated. No residue was obtained. (The desired product should be soluble in alcohol by analogy with IV).

10-Amino-x-chloro-6-methoxypyrido(4.3-b)quinoline (VIII). 3-(*p*-Methoxyphenylamino) isonicotinic acid, 2.4 g., and phosphorus oxychloride, 50 g., were refluxed for two hours, the red solution partially distilled under vacuum and then poured into a mixture of ice, chloroform, and dilute ammonia. The organic constituents were extracted with chloroform, stirred with potassium carbonate on a cold water-bath, and then allowed to dry overnight with fresh carbonate. The red chloroform solution (smelling of ammonia) was chromatographed through a mixture of Hyflo and alumina. Only a brownish-orange diffuse band was noted. After several fractional crystallizations from the chloroform solution (Norit) a yellow crystalline material, m.p. 261–262° (d.) was obtained.

Anal. Calc'd for $C_{13}H_{10}ClN_3O$: Cl, 13.68; N, 16.19.

Found: Cl, 13.75, 13.61; N, 16.36, 16.25.

The position occupied by the chlorine atom was not determined, although it was assumed to be in the benzene ring. The chlorine was not present as a hydrochloride since it was not removed by warm 2 *N* sodium hydroxide.

SUMMARY

Several pyrido(4.3-b)quinolones and 4-substituted-amino-2,6-dimethylnicotinic acids have been prepared and tested pharmacologically.

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ALIPHATIC FLUORIDES. I. ω,ω'-DIFLUOROALKANES

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The strength of the carbon-fluorine bond, calculated by the postulate of the additivity of normal covalent bonds (1), is 61.1 kcal./mole. This is smaller by 45.9 kcal. than the somewhat empirical value of 107 kcal. given by Pauling for the actual bond strength. The additional energy is accounted for by the resonance theory, according to which structures of an ionic type as well as the covalent type contribute resonance energy (1). In accordance with these considerations, the high ionic resonance energy of the carbon-fluorine bond should lead us to expect a much greater stability for this bond than for the carbon-to-halogen bond of the other corresponding alkyl halides. However, Henne and Midgley (2) describe the *n*-alkyl fluorides as less stable, showing a tendency to lose hydrogen fluoride with formation of olefins. According to these authors, only the first members of the homologous series up to *n*-pentyl fluoride are described as stable to distillation at normal pressure. Higher members of this series exhibit a tendency to "decompose spontaneously to hydrogen fluoride and ethylenic hydrocarbons", an opinion which has found its way into several textbooks. This statement, however, is in contradiction to the observations of Desreux (3), who describes *n*-hexyl and *n*-heptyl fluoride as compounds which are completely stable to distillation at atmospheric pressure and are not attacked by sodium amalgam, concentrated alkali, or phosphorus pentoxide. They are affected only by concentrated sulfuric acid. As proof for the lower stability of *n*-alkyl fluorides, Henne and Midgley cite the toxicity of ethyl fluoride which, when applied as an inhalation anesthetic in large doses, causes fatal oedema in the lungs and the upper respiratory tract of animals similar to that caused by hydrogen fluoride. However, the physiological activity of any chemical compound should not be evaluated as proof of its instability, since living cells are able to perform chemical reactions which often cannot be reproduced *in vitro*.

The inertness of primary bound fluorine in aliphatic compounds toward sodium ethoxide, alkalies, and dilute acids has been observed frequently in connection with other problems. Under similar conditions the corresponding chlorine compounds have been found to be considerably more reactive. Ethylene fluoride is described (2) as decomposing spontaneously to hydrogen fluoride and butadiene at 0° and as hydrolyzing to glycol by merely passing it through water. Since no other members of the homologous series of the ω,ω'-difluoroalkanes of the general formula $F(CH_2)_{n>2}F$ have been described thus far, it appeared interesting to prepare some of the lower members and to determine their chemical and physical properties.

There exist a variety of methods for preparing these compounds by exchange of the halogen in the corresponding dichloro- or dibromo-alkanes with the fluorine in certain inorganic metal fluorides. Of these methods, the fluorination

with anhydrous potassium fluoride in glycol (4) was chosen, not only because of the availability of anhydrous potassium fluoride, but also because of the desirability of determining the scope of the application of this fluorinating agent.

The method can be applied successfully to the preparation of the desired difluoroalkanes except ethylene fluoride, which could not be prepared by this method. In addition to traces of vinyl fluoride, the only fluorination product of ethylene bromide is 1-bromo-2-fluoroethane which is obtained in about 24% yield. The main product of the reaction of potassium fluoride with ethylene bromide in glycol is vinyl bromide, formed by dehydrobromination of the starting material. Using ethylene chloride as reactant the results are even more unsatisfactory.

Since the fluorinated product is distilled off during the reaction at the same rate at which it is formed, and since the required reaction temperatures of 160–180° for chlorides and of 130–150° for the bromides do not allow much variation of the reaction conditions, it is necessary to add the aliphatic halides (especially

TABLE I

FLUORINATION OF DIHALOGENOALKANES

STARTING MATERIAL	REACTION TEMP. °C.	DIST. TEMP. °C.	DIFLUORO-ALKANE %	YIELDS OF HALOGENO-FLUORO-ALKANE %	FLUORO-ALKENE %
$BrCH_2CH_2Br$	150	40–50	—	23.7	—
$BrCH_2CH_2CH_2Br$	150	45–55	23.3	6.2	19.4
$ClCH_2(CH_2)_2CH_2Cl$	170	104–116	44.2	6.6	2.2
$ClCH_2(CH_2)_3CH_2Cl$	180	130–138	36.6	9.4	2.8
$ClCH_2(CH_2)_4CH_2Cl$	185	140–150	30.0	—	2.5

the lower-boiling ones) slowly at the same rate at which they are consumed. Otherwise, the temperature of the reaction mixture is lower than the required reaction temperature and fluorination takes place only to a small extent.

Together with the desired difluoroalkanes, which are obtained in yields of 26–44%, there are also formed the monofluorinated derivatives in small amounts and traces of ω-fluoroalkene-1, formed by dehydrohalogenation of the monofluoro derivative. Table I shows the reaction temperatures, distillation temperatures, and yields of the various fluorine compounds for the fluorination of the homologous dibromo- or dichloro-alkanes.

The ω,ω'-difluoroalkanes are colorless liquids having an odor which resembles that of the lower liquid hydrocarbons. Their boiling points are in good agreement with the lowering of the boiling point (38° on the average) generally observed when chlorine is substituted by fluorine in aliphatic compounds. They are completely stable to distillation at atmospheric pressure and showed no sign of decomposition within a year's period. Chemically they are unreactive; they do not react at reflux temperature with magnesium in ether, sodium iodide in acetone, sodium ethoxide in absolute ethanol, aqueous-alcoholic potassium hydroxide, potassium carbonate in absolute ethanol, or dilute acids. An exception

is 1,3-difluoropropane, which shows considerable reactivity towards sodium ethoxide, whereas the higher homologs exhibit only negligible reactivity. However, the reactivity of difluoropropane is not more than 20% of that of the corresponding chlorine compound.

In order to compare the reactivity of primary bound fluorine with that of chlorine in aliphatic compounds, the corresponding difluoro- and dichloroalkanes have been treated with sodium ethoxide in ethanol and with aqueous-alcoholic potassium hydroxide under the same conditions, and the reacted halogen present as ions has been determined titrimetrically. In the first series of determinations, 0.01 mole of the substance was refluxed with 25 ml. of 1 *N* sodium ethoxide solution in ethanol for 30 minutes, and the mixture was then

TABLE II

REACTIVITY OF ω,ω'-DICHLORO- AND DIFLUORO-ALKANES

SUBSTANCE $X(CH_2)_nX$	1 *N* NaOEt		1 *N* KOH	
	X = Cl	X = F	X = Cl	X = F
n = 2	49.5[a]	—	42.2[c]	—
= 3	57.0	11.6[b]	26.3	0.9[d]
= 4	38.3	0.2	20.4	.2
= 5	31.4	0.1	15.4	.2
= 6	28.7	0.2	12.1	.2
$C_6H_{13}X$	21.2	traces	6.7	.2

[a] Percentage of chlorine reacted after refluxing 0.01 mole of substance with 25 ml. of 1 *N* $NaOC_2H_5$ in ethanol for 30 minutes.

[b] Percentage of fluorine reacted under the same conditions as in *a*.

[c] Percentage of chlorine reacted after refluxing 0.01 mole of substance with 25 ml. of 1 *N* KOH in 70% ethanol for 30 minutes.

[d] Percentage of fluorine reacted under the same conditions as in *c*.

diluted with water and the halogen ions titrated. In another series the halogen ions were determined after refluxing 0.01 mole of the substance with 25 ml. of 1 *N* potassium hydroxide solution in 70% ethanol. The results in Table II show the percentage of halogen present as ions after the reaction calculated on the total amount of halogen in the molecule. For comparison *n*-hexyl chloride and fluoride have been included in these two series.

As can be seen from Table II the reactivity of the C—Cl bond is increased by the presence of a second C—Cl bond in the molecule. While the dichloroalkanes from the C_2 to the C_6 members show a steady decrease in reactivity towards aqueous-alcoholic potassium hydroxide approaching the value of *n*-hexyl chloride, this decrease is interrupted by a maximum at the C_3 derivative in their reactivity towards sodium ethoxide. This increased reactivity of the chlorine might be caused by simultaneous dehydrochlorination of the molecule, together with the normal substitution reaction: $RCl + {}^-OC_2H_5 \rightarrow ROC_2H_5 + Cl^-$. The hydrogen on the center carbon atom of this molecule is expected to be highly acid due to the inductive effect of the chlorine on both the adjacent carbon atoms.

1,3-Difluoropropane also shows an increased reactivity towards sodium ethoxide as compared to its higher homologs, because of the same reasons pointed out or 1,3-dichloropropane. The data obtained for the reactivity of the primary bound fluorine prove definitely that it is much more stable towards alkaline reactants than chlorine in the corresponding chlorine compounds. Ethylene fluoride has not been included in this investigation, since it could not be obtained by halogen exchange with potassium fluoride from ethylene bromide or chloride. By extrapolation from the reactivities of the higher difluorides and the dichlorides including ethylene chloride, however, the reactivity of ethylene fluoride should be expected not to exceed 10% of the total fluorine content of the molecule under the above described conditions. However, this is not in agreement with the reported properties of ethylene fluoride (2) and re-investigation of its stability seems necessary, since several compounds which have been described as decomposing spontaneously have been found in this laboratory to be completely stable.

TABLE III

PHYSICAL CONSTANTS OF NEW COMPOUNDS

SUBSTANCE	B.P. AT 760 MM. °C.	d_4^{25}	d_4^{35}	t	n_D^t	MR_D [a]	AR_F [b]
$F(CH_2)_3F$	41.6	1.0057	0.9908	26.0	1.3190	15.77	0.96
$F(CH_2)_4F$	77.8	0.9767	0.9648	25.0	1.3433	20.38	.97
$F(CH_2)_5F$	105.5	0.9572	0.9463	23.8	1.3618	25.01	.96
$F(CH_2)_6F$	129.9	0.9407	0.9310	25.0	1.3739	29.65	.97
$F(CH_2)_3CH{:}CH_2$	61.9–62.1	—	—	—	—	—	—
$F(CH_2)_4CH{:}CH_2$	91–92	—	—	26.0	1.3869	—	—
$Br(CH_2)_3F$	101.4	1.542	1.525	23.0	1.4295	23.56	.82
$Cl(CH_2)_4F$	114.7	1.0627	1.0508	23.0	1.4025	25.31	.86
$Cl(CH_2)_5F$	143.2	1.0325	1.0219	23.0	1.4120	29.96	.90
$BrCH_2CHBrCH_2F$ [c]	162.5	2.089	2.082	23.0	1.5092	31.43	.95

[a] MR_D is the molecular refraction for the sodium-D line calculated by the Lorentz-Lorenz equation. [b] AR_F is the atomic refraction for fluorine, computed by substracting the increments for C (2.418), H (1.100), Cl (5.967), and Br (8.865) from MR_D. [c] Reported by Meslans (5): b.p. 158–159°, d^{18} 2.09.

Since the reactivity of the ω,ω'-difluoroalkanes is extremely low, an activating effect of the carbon-fluorine bonds on each other can only be observed in the trimethylene derivative. The values obtained for the reactivity of fluorine in the higher homologs fall within the limits of error of the method used, but they show definitely that the carbon-fluorine bond in these compounds is less reactive (by two orders of magnitude) than the primary aliphatic carbon-chlorine bond.

It is to be expected that the ω-halogeno-1-fluoroalkanes, which are formed as by-products in the preparation of the difluoroalkanes, can become the main reaction products of the fluorination of dihalogenoalkanes by proper choice of the reaction conditions. They are the first step of the fluorination, the second step of which is the formation of the difluoroalkanes. Dehydrohalogenation of

the intermediate, however, competes with this normal reaction and yields ω-halogeno-1-alkene as by-product. This side reaction prevailed in the fluorination of 1,3-dihalogenopropane, resulting in high yields of allyl fluoride which was characterized by its bromine addition product. The 1,2-dibromo-3-fluoropropane obtained had a somewhat higher boiling point than that given by Meslans (5) (158–159°). Its physical constants are listed in Table III. The dehydrohalogenation, which becomes of minor importance with the higher dihalides, is probably caused by the mutual influence of the two strongly electronegative substituents. The physical properties of the halogenofluoroalkanes are given in Table III together with those of the difluoroalkanes and two of the higher fluoroalkenes. A preliminary qualitative investigation of their chemical properties showed that the reactivity of the halogen atom corresponds to that of the halogen in the corresponding dihalides, while the carbon-fluorine bond exhibits approximately the same low reactivity as in the difluorides. Since the chlorofluoroalkanes are, therefore, valuable intermediates for the introduction of ω-fluoroalkyl groups into organic molecules, their preparation and chemical properties are under investigation and will be the subject of another paper.

EXPERIMENTAL PART

Materials. Potassium fluoride, KF. The anhydrous salt used as fluorinating agent was the commercial product in flakes procured from Harshaw Chemical Co. It was kept in a drying oven at 125° for 24 hours before grinding in a ball mill. The powdered salt was dried immediately before use in a vacuum oven at 150° for 24 hours in order to remove the last traces of moisture.

Ethylene glycol. To obtain the solvent for the potassium fluoride anhydrous, the commercial product (DuPont) was distilled at 50 mm. pressure until the boiling point was constant over a considerable period of time. About 10% of the commercial product was distilled off and discarded. The remaining part was used as the solvent in the fluorination reaction.

ω,ω′-Dihalogenoalkanes. All dihalogenoalkanes, except 1,6-dichlorohexane, used as starting materials for the preparation of the difluoroalkanes were commercial products which were distilled before use. 1,6-Dichlorohexane (b.p. 55° at 0.5 mm. pressure) was obtained by treatment of 1,6-hexanediol with thionyl chloride in the presence of pyridine.

Preparation of difluoroalkanes. Since the preparation of the difluoroalkanes is similar in all cases and differs only in the temperatures of the reaction mixture and the temperature at which the reaction product distills, the preparation of 1,5-difluoropentane is described as a typical example in the following. The total yield of fluorinated product is generally about 50% and consists mainly of ω,ω′-difluoroalkanes, varying quantities of 1-halogeno-ω-fluoroalkane, and a small amount of ω-fluoro-1-alkene. The reaction temperatures and yields of the various reaction products are given in Table I. The physical constants and analytical data of nine new primary aliphatic fluorides are listed in Table III.

Fluorination of 1,5-dichloropentane. A mixture of 290 g. (5 moles) of finely powdered, anhydrous potassium fluoride and 275 g. of ethylene glycol was heated at 180° in a 1-liter, 3-neck round-bottomed flask, fitted with a mercury-sealed stirrer, dropping-funnel, and a 12-cm. column with attached condenser and receiver. To the vigorously stirred reaction mixture there was added 281 g. of 1,5-dichloropentane in the course of 4 hours at such a rate that the reaction products distilled at 130–138°. After addition of the dichloropentane was complete, a slow stream of air was sucked through the apparatus for half an hour in order to distill off the reaction product completely. Together with the reaction products some glycol distilled over; the upper layer consisting of fluorinated product was separated

and treated with calcium chloride and sodium fluoride overnight. After filtration, the colorless liquid (137.2 g.) was fractionated at atmospheric pressure through a 75-cm. 3-step Vigreux column yielding 5.0 g. of 5-fluoro-1-pentene at 61–62.5°, 79.1 g. of 1,5-difluoropentane at 104–106°, 23.4 g. of 1-chloro-5-fluoropentane at 139–144°; 23.2 g. or 8.2% of unreacted 1,5-dichloropentane was recovered.

The analytical data of the new compounds are listed in Table IV.

TABLE IV

ANALYTICAL DATA OF NEW COMPOUNDS

SUBSTANCE	CALC'D C	FOUND C	CALC'D H	FOUND H	CALC'D F	FOUND F
$F(CH_2)_3F$	45.0	44.6	7.6	7.4	47.5	47.4
$F(CH_2)_4F$	51.1	51.1	8.6	8.5	40.4	40.3
$F(CH_2)_5F$	55.5	55.5	9.3	9.3	35.1	35.0
$F(CH_2)_6F$	59.0	58.8	9.9	9.8	31.1	30.9
$F(CH_2)_3CH{:}CH_2$	68.1	67.9	10.3	10.5	—	—
$F(CH_2)_4CH{:}CH_2$	70.5	70.2	10.9	10.6	18.6	18.5
$Br(CH_2)_3F$	25.6	25.5	4.3	4.4	13.5	13.4
$Cl(CH_2)_4F$	43.5	43.5	7.3	7.2	17.2	17.1
$Cl(CH_2)_5F$	48.2	48.1	8.0	8.1	—	—

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SUMMARY

Four members of the series of ω,ω'-difluoroalkanes of the general formula $F(CH_2)_nF$ ($n = 3, 4, 5,$ and 6) have been prepared and their chemical and physical properties determined. The primary carbon-fluorine bond in these compounds exhibits the stability expected according to considerations of the resonance theory.

The reactivity of primary bound fluorine in aliphatic compounds has been shown to be extremely low as compared to that of chlorine in the corresponding chlorine compounds.

1-Bromo-3-fluoropropane, 1-chloro-4-fluorobutane, 1-chloro-5-fluoropentane, 5-fluoro-1-pentene, and 6-fluoro-1-hexene have been obtained as by-products of the preparation of the difluoroalkanes. Their physical constants are tabulated.

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[Contribution from the Department of Chemistry, University of Notre Dame]

THE PREPARATION OF SEVERAL CHLORINATED 1-VINYLNAPHTHALENES[1]

CHARLES C. PRICE and SING-TUH VOONG[2]

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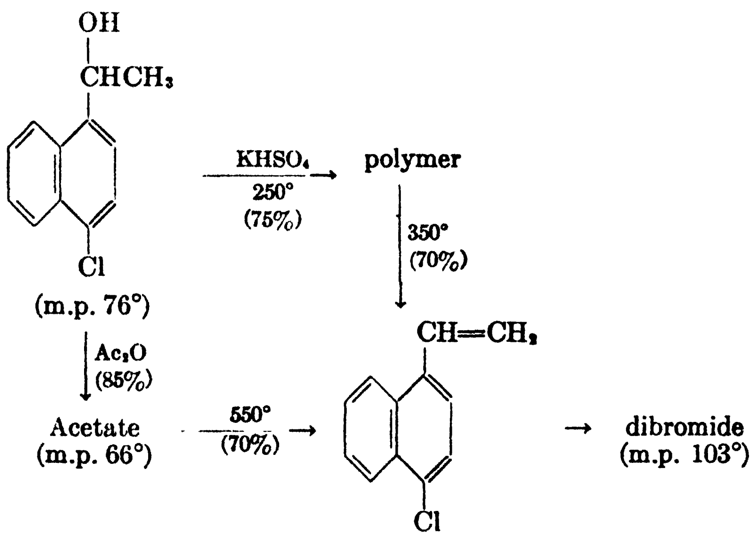
There are a number of reports of the preparation of 1-vinylnaphthalene by various routes (1–8). It was the purpose of the investigation reported herein to prepare a number of chlorinated derivatives for comparison. Those described are the 4-, 5-, and 7-chloro-, and 5,8-dichloro-1-vinylnaphthalenes.

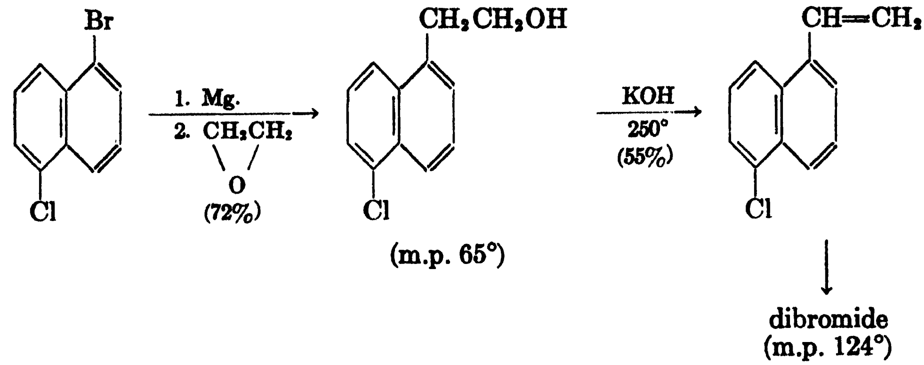
The 4-chloro compound was prepared from 1-chloronaphthalene through Friedel-Crafts acetylation, reduction to the arylmethylcarbinol, and dehydration. The dehydration was effected conveniently by pyrolysis of the acetate or by "dehydration-polymerization" over potassium acid sulfate followed by thermal depolymerization, which proceeded smoothly and in good yield.



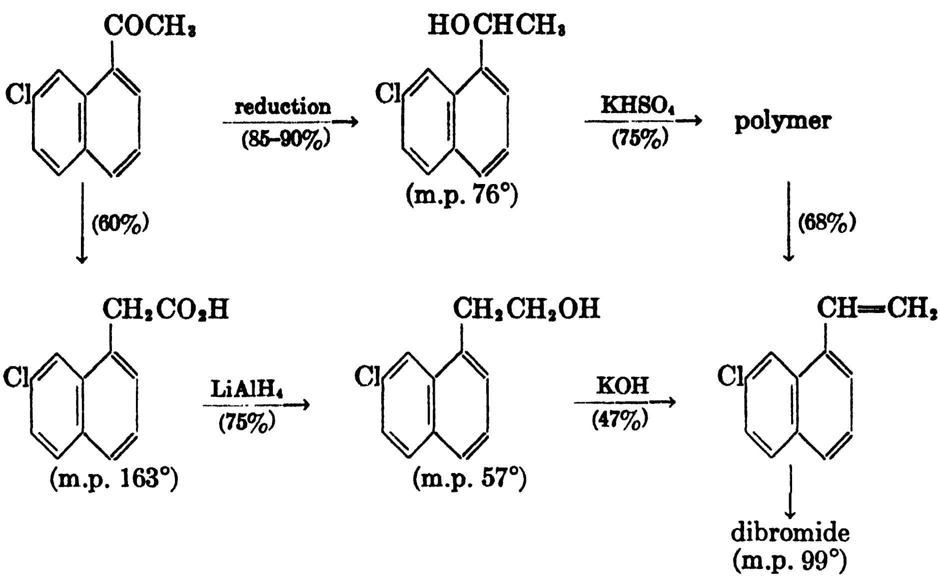
The 5-chloro isomer was prepared from 1-nitronaphthalene through bromination to the 5-bromo derivative. The latter was obtained in 85% yield, a considerable improvement over the 25% reported by Shoesmith (9) and Campbell (10). Reduction and a Sandmeyer reaction produced 1-bromo-5-chloronaphthalene, which was converted to the vinyl compound through the following steps.

[1] Abstracted from a Ph.D. thesis submitted to the graduate school of the University of Notre Dame.

[2] General Tire and Rubber Company Fellow, 1946–1948.

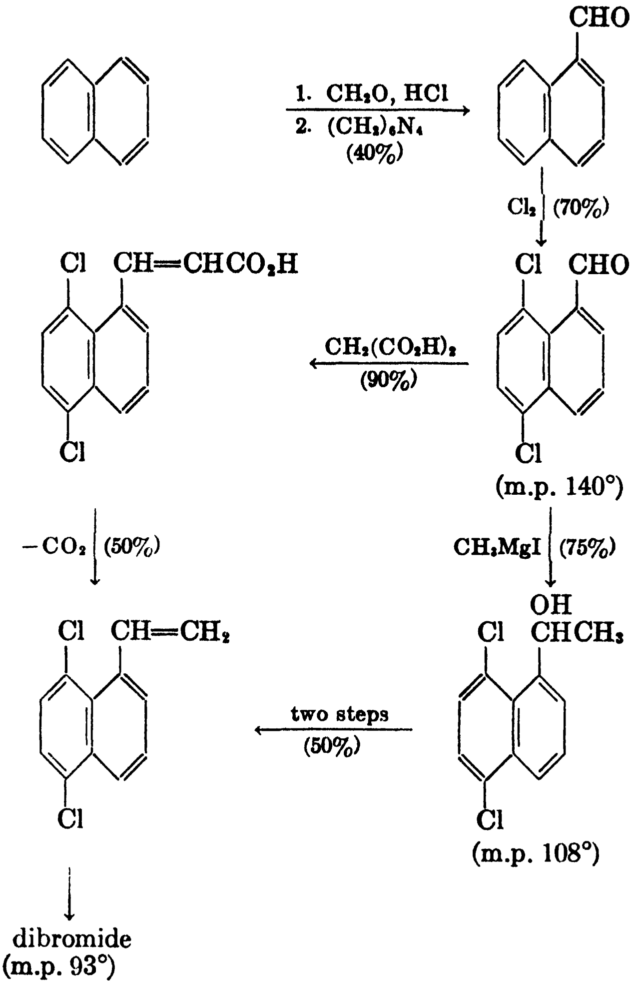


The 7-chloro isomer was prepared through Friedel-Crafts acetylation of 2-acetaminonaphthalene (11). The 7-chloro ketone was then converted to the vinyl compound either by conventional reduction and acid dehydration of the secondary carbinol or by converting to the naphthylacetic acid followed by reduction and alkaline dehydration of the primary carbinol.



5,8-Dichloro-1-vinylnaphthalene was prepared through chlorination of 1-naphthaldehyde *via* two routes, one by addition of methylmagnesium iodide followed by dehydration, the other by condensation with malonic acid followed by decarboxylation.

The preparation of 1-naphthaldehyde from naphthalene was simplified considerably by not isolating the intermediate chloromethyl derivative, depending on purification of the aldehyde through its sodium bisulfite addition compound to separate unreacted naphthalene.



EXPERIMENTAL[3]

(4-Chloro-1-naphthyl)methylcarbinol was prepared by aluminum isopropoxide reduction of 4-acetyl-1-chloronaphthalene, [b.p. 165–168° (4–5 mm.)], prepared and purified through the picrate (m.p. 87–88°) according to Jacobs and co-workers (12). Reduction of 210 g. of the ketone with 200 g. of aluminum isopropoxide in 1000 ml. of isopropyl alcohol required 5 to 6 hours at 55–60°. After evaporation of most of the solvent, the mixture was hydrolyzed with dilute hydrochloric acid and extracted with ether. Evaporation of the dried ether extract left 195–204 g. (90–93%) of white solid, m.p. 70–71°. Recrystallization from *n*-hexane gave long needles, m.p. 75.5–76°.[4]

Anal. Calc'd for $C_{12}H_{11}ClO$: C, 69.72; H, 5.36; Cl, 17.18.
Found: C, 69.56; H, 5.26; Cl, 17.78.

The 3,5-dinitrobenzoate melted at 130–131° after recrystallization from *n*-hexane.

Anal. Calc'd for $C_{19}H_{13}ClN_2O_7$: N, 6.99. Found: N, 6.69.

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[3] Analyses by Micro-Tech Laboratories, Skokie, Ill.

[4] Mowry, Renoll, and Huber (8) reported this carbinol as a liquid, n_D^{25} 1.6200.

The *acetate*, prepared in 85% yield by refluxing the carbinol in acetic anhydride, crystallized from *n*-hexane as long needles, m.p. 65–66°, b.p. 168–170° (2–3 mm.).

Anal. Calc'd for $C_{14}H_{13}ClO_2$: C, 67.59; H, 5.27; Cl, 14.27.
Found: C, 67.55; H, 5.52; Cl, 14.70.

Dehydration of (4-chloro-1-naphthyl)methylcarbinol by the usual procedure, heating at 250° over potassium sulfate under 30–40 mm., gave only a 16% yield of vinyl compound, the major product consisting of an undistilled residue of transparent resin. By raising the pressure to over 50 mm., no vinyl compound was obtained, only resin. This product of "dehydration-polymerization" was then purified by precipitation with methanol from benzene solution to give a 75% yield of white powdery polymer.

Depolymerization was accomplished by heating in a sand bath at about 350° under 0.5–1.0 mm. pressure to yield 65–75% of *4-chloro-1-vinylnaphthalene*, b.p. 124–125° (0.5–1 mm.). Pyrolysis of the acetate (containing a small amount of sulfur) at 550° gave the vinyl compound in 71% yield.

The *dibromide* was prepared by adding bromine in carbon tetrachloride. After recrystallization from 80% ethanol, the product melted at 102–103°.

Anal. Calc'd for $C_{12}H_9Br_2Cl$: Halogen, 56.05. Found: Halogen, 55.50.

Polymerization of 4-chloro-1-vinylnaphthalene by heating at 60° with 1% benzoyl peroxide gave a hard, transparent polymer. After reprecipitation from benzene by methanol, it was found to soften at 170–172°.

Anal. Calc'd for $(C_{12}H_9Cl)_n$: C, 76.37; H, 4.81; Cl, 18.81.
Found: C, 75.80; H, 5.10; Cl, 18.84.

5-Bromo-1-nitronaphthalene was prepared by adding 640 g. of bromine to 684 g. of 1-nitronaphthalene and 4.5 g. of ferric chloride warmed to 80–90° on a water-bath. After washing with water and 10% bicarbonate, recrystallization from ethanol yielded 800–850 g. (80–85%) of yellow needles, m.p. 120°, a considerable improvement of the 25% yield previously reported (9, 10).

This was converted to *1-bromo-5-chloronaphthalene* by reduction with stannous chloride, diazotization and treatment with cuprous chloride to yield 51% of product, m.p. 115–116° (13).

2-(5-Chloro-1-naphthyl)ethanol. A solution of 120 g. (0.5 mole) of 5-bromo-1-chloronaphthalene and a small crystal of iodine in 150 ml. of ether and 150 ml. of benzene was stirred while 12 g. (0.5 mole) of magnesium turnings was added slowly. When the Grignard preparation was complete, the mixture was cooled to −5° and 20 g. (0.45 mole) of ethylene oxide in 50 ml. of ether was added at 0°. After an hour of reflux, hydrolysis, washing, drying, and evaporation left the solid alcohol, 75 g. (72%), which was recrystallized from hexane, m.p. 64–65°.

Anal. Calc'd for $C_{12}H_{11}ClO$: Cl, 17.18. Found: Cl, 17.55.

The *phenylurethan* was recrystallized from cyclohexane, m.p. 144–145°.

Anal. Calc'd for $C_{19}H_{16}ClNO_2$: Cl, 10.88. Found: Cl, 11.43.

The *p-nitrobenzoate* crystallized from ethanol as colorless needles, m.p. 134–135°.

Anal. Calc'd for $C_{19}H_{14}ClNO_4$: Cl, 10.01. Found: Cl, 10.76.

5-Chloro-1-vinylnaphthalene. A mixture of 40 g. of the alcohol above and 25 g. of potassium hydroxide was heated to 250–260° under 35–40 mm. pressure, yielding 21 g. (55%) of vinyl compound, b.p. 142–144° (2–3 mm.).

The *dibromide* formed yellow crystals, m.p. 122–124°.

Anal. Calc'd for $C_{12}H_9Br_2Cl$: Halogen, 56.05. Found: Halogen, 56.20.

The *polymer* was a yellow powder with a softening point of about 180–185°.

Anal. Calc'd for $(C_{12}H_9Cl)_n$: Cl, 18.81. Found: Cl, 19.00.

7-Amino-1-acetonaphthone was obtained in 60–70% yields as golden-yellow rhombic needles, m.p. 110–111° (13). Diazotization and treatment with cuprous chloride gave an unpromising-looking black tarry solid which, surprisingly, produced a colorless solid on distillation. One recrystallization from ethanol gave 166 g. (65%) of 7-chloro-1-acetonaphthone, m.p. 65–66°, b.p. 158–160° (4 mm.) (14).

(7-Chloro-1-naphthyl)methylcarbinol was obtained in 90–92% yield by aluminum iso-

propoxide reduction and in 85% yield by lithium aluminum hydride. It crystallized from *n*-hexane as needles, m.p. 75–75.5°.

Anal. Calc'd for $C_{12}H_{11}ClO$: Cl, 17.18. Found: Cl, 17.52.

The *phenylurethan* crystallized from ethanol as colorless needles, m.p. 228–230°.

Anal. Calc'd for $C_{19}H_{16}ClNO_2$: Cl, 10.88. Found: Cl, 10.56.

The *p-nitrobenzoate* was obtained as rhombic crystals from ethanol, m.p. 111–112°.

Anal. Calc'd for $C_{19}H_{14}ClNO_4$: Cl, 10.01. Found: Cl, 10.45.

7-Chloro-1-vinylnaphthalene. Again, the direct potassium acid sulfate dehydration gave principally polymer and only a poor yield (20%) of vinyl compound at low pressure, so the "dehydration-polymerization" procedure at 230–240° under 40 mm. of pressure was used to produce reprecipitated polymer in 75% yield, softening point 190–192°.

Anal. Calc'd for $(C_{12}H_9Cl)_n$: Cl, 18.81. Found: Cl, 18.92.

The *monomer* was obtained in 68% yield by pyrolysis at 400–450° under 4–5 mm. pressure, b.p. 120–121° (4–5 mm.).

7-Chloro-1-naphthylacetic acid. A mixture of 10 g. of 7-chloro-1-naphthyl methyl ketone, 2.5 g. of sulfur and 6.5 g. of morpholine was boiled gently under reflux for 16 hours. The crude thiomorpholide was hydrolyzed in a mixture of acetic and sulfuric acids and the resulting acid purified from benzene-*n*-hexane to give 6.0–6.5 g. (55–60%) of needles, m.p. 162–163°.

Anal. Calc'd for $C_{12}H_9ClO_2$: Cl, 16.18. Found: Cl, 16.60.

2-(7-Chloro-1-naphthyl)ethanol. A sample of 11 g. (0.05 mole) of the above acid was placed in the thimble of a Soxhlet extractor and a solution of 2.85 g. (0.05 mole) of lithium aluminum hydride in the flask. The mixture was refluxed until all the acid had dissolved. After hydrolysis and washing, the ether layer was evaporated. The residue crystallized from ethanol as needles, 8 g. (75%), m.p. 55–57°.

Anal. Calc'd for $C_{12}H_{11}ClO$: Cl, 17.18. Found: Cl, 17.68.

The phenylurethan was recrystallized from ethanol, m.p. 138–139°.

Anal. Calc'd for $C_{19}H_{16}ClNO_2$: Cl, 10.88. Found: Cl, 11.05.

The *p-nitrobenzoate* was also recrystallized from ethanol, m.p. 140–141°.

Anal. Calc'd for $C_{19}H_{14}ClNO_2$: Cl, 10.01. Found: Cl, 10.25.

7-Chloro-1-vinylnaphthalene. Dehydration of the alcohol was accomplished by heating 8 g. with 2.5 g. of potassium hydroxide to 240–250° under 30–40 mm. pressure to yield 3.5 g. (47%) of vinyl compound.

The *dibromide* formed colorless crystals, m.p. 98–99°.

Anal. Calc'd for $C_{12}H_9Br_2Cl$: Halogen, 56.05. Found: Halogen, 55.80.

1-Naphthaldehyde can be prepared satisfactorily by chloromethylation of naphthalene (15) followed by the Sommelet reaction (16, 17). The troublesome separation of naphthalene from its chloromethyl derivative was successfully avoided by carrying out the Sommelet reaction on the crude product prepared according to "Organic Syntheses" (15), relying on the aldehyde-bisulfite addition compound for purification. The crude chloromethylation mixture from 256 g. of naphthalene was dissolved in 400 ml. of boiling glacial acetic acid and treated with 120 g. of urotropine. After cooling, the mixture was poured into 1.5 l. of cold water with good stirring. The crude 1-naphthaldehyde was extracted with 800 ml. of ether which, after washing with 5% sodium bicarbonate and water, was shaken vigorously for half an hour with 400 ml. of 40% sodium bisulfite and 100 ml. of 95% ethanol. The precipitate was washed thoroughly with ether. Addition to 10% sodium carbonate liberated the aldehyde, which was separated by extraction with ether and distilled, b.p. 140–142° (8 mm.); yield, 105–125 g. (34–40%).

5,8-Dichloro-1-naphthaldehyde was prepared by chlorinating 60 g. of 1-naphthaldehyde in 90 ml. of chloroform in the presence of 0.5 g. of ferric chloride at 55–60°. After washing the product in benzene solution, evaporation left a solid which was recrystallized from hexane as pale yellow, short needles, m.p. 136–137°; yield, 55–60 g. (65–70%). Recrystallization from benzene-hexane with charcoal decolorization produced colorless needles of 5,8-dichloronaphthaldehyde, m.p. 139–140°.

Anal. Calc'd for $C_{11}H_6Cl_2O$: Cl, 31.20. Found: Cl, 31.11.

During recrystallization, it was possible to isolate very small amounts of two *by-products*, one, short, yellow needles, m.p. 124–125°, was believed to be the monochloro (5- or 8-?) derivative. The other, a yellow powder, m.p. 235°, gave the proper chlorine analysis for a dichloronaphthoic acid (%Cl: calc'd 29.00; found, 28.66).

The *anil* formed readily on warming the aldehyde with aniline in ethanol. After recrystallization from hexane, it melted at 140–141°. Digestion with methanol raised the melting point to 144.5–145°.

Anal. Calc'd for $C_{17}H_{11}Cl_2N$: C, 68.05; H, 3.66; N, 4.70; Cl, 23.60.
Found: C, 68.17; H, 3.89; N, 4.71; Cl, 23.54.

Digestion of the anil in 10% hydrochloric acid regenerated *aldehyde* which, after recrystallization from methanol, melted at 140–140.5° and gave a 20° depression on mixing with the anil.

The *semicarbazone* separated from ethanol as colorless needles, m.p. 234–235°.

Anal. Calc'd for $C_{12}H_9Cl_2N_3O$: N, 14.90. Found: N, 14.52.

The *oxime* also separated from ethanol as colorless needles, m.p. 199–200°.

Anal. Calc'd for $C_{11}H_8Cl_2NO$: N, 5.96. Found: N, 5.85.

The *structure* of the aldehyde was established by oxidation of a 1-g. sample in pyridine solution by addition of aqueous alkaline potassium permanganate. After boiling for two hours, the solution was filtered and then washed with three portions of chloroform. Acidification of the aqueous layer precipitated 0.75 g. of white solid, m.p. 187–188°, in agreement with that reported for 5,8-dichloronaphthoic acid (18).

(5,8-Dichloro-1-naphthyl)methylcarbinol was prepared from 22.5 g. of the aldehyde by addition to the Grignard reagent prepared in ether from 15.1 g. of methyl iodide and 2.43 g. of magnesium. After hydrolysis, the ether solution was washed with water, 5% sodium bicarbonate, 40% sodium bisulfite and water, dried, and evaporated. The solid residue was recrystallized from cyclohexane to yield 17–18 g. (70–75%) of colorless rhombic crystals, m.p. 107–107.5°.

Anal. Calc'd for $C_{12}H_{10}Cl_2O$: C, 59.75; H, 4.18; Cl, 29.00.
Found: C, 59.70; H, 4.30; Cl, 29.00.

The *p-nitrobenzoate* crystallized from ethanol as yellow plates, m.p. 149–150°.

Anal. Calc'd for $C_{19}H_{13}Cl_2NO_4$: N, 3.59. Found: N, 3.59.

Dehydration-polymerization with potassium bisulfate at 240–250° for three hours under 45 mm. pressure gave a 70% yield of reprecipitated polymer. This was depolymerized by heating at 400–450° under 0.5–1.0 mm. pressure to yield 67–75% of 5,8-dichloro-1-vinylnaphthalene, b.p. 150–152° (2–3 mm.). The *dibromide* crystallized from 80% ethanol as yellow needles, m.p. 92–93°.

Anal. Calc'd for $C_{12}H_8Br_2Cl_2$: Halogen, 60.31. Found: Halogen, 59.58.

The polymer was obtained as a yellow powder, softening point 120–130°.

Anal. Calc'd for $(C_{12}H_8Cl_2)_n$: Cl, 31.84. Found: Cl, 31.51.

β-(5,8-Dichloro-1-naphthyl)acrylic acid was prepared by refluxing 12 g. of the aldehyde, 8 g. of malonic acid, and a few drops of piperidine in 60 ml. of dry pyridine for six hours. After cooling, the mixture was poured into 20% sulfuric acid. The solid was collected and recrystallized from methanol or aqueous ethanol with decolorization, to yield 12.5–13.0 g. (85–90%) of colorless short needles, m.p. 258–259°, with some decomposition.

Anal. Calc'd for $C_{13}H_8Cl_2O_2$: C, 58.50; H, 3.00.
Found: C, 58.55; H, 2.96.

Decarboxylation to the vinyl compound was accomplished by heating to 225° in quinoline containing copper powder and hydroquinone; yield, 45%. Substituting acridine for quinoline raised the yield to 51%.

SUMMARY

4-Chloro-, 5-chloro-, 7-chloro-, and 5,8-dichloro-1-vinylnaphthalenes and a number of intermediates and derivatives have been prepared and characterized.

All four vinyl compounds polymerize readily to hard resins, the 7-chloro polymer having the highest, the 5,8-dichloro the lowest softening point.

NOTRE DAME, INDIANA

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[From the Department of Chemistry, Vanderbilt University]

THE BECKMANN REARRANGEMENT. THE REARRANGEMENT OF SOME SUBSTITUTED ACETOPHENONE OXIMES IN SULFURIC ACID

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GENERALIZATIONS

The Beckmann rearrangement has been justifiably called the "Mona Lisa" of rearrangements. Meisenheimer, Kuhara, and Chapman have made outstanding contributions to the understanding of the reaction, while Blatt (1) and Jones (2) have adequately summarized the countless experiments of these and other workers. Nevertheless, some of the generalizations that have grown from their studies and become accepted almost as axioms to explain all phenomena of the Beckmann rearrangement, were originally based on specialized and sometimes limited reactions which may not apply generally. Chapman's work, for instance, was based on the rates of rearrangement of oxime picryl ethers in polar organic solvents (3, 4), which is a quite different environment than sulfuric acid or phosphorus pentachloride in ether, the usual rearrangement media. It is the purpose of this paper and subsequent ones to apply the concepts of Chapman *et al.* to more practical conditions, and to confirm or modify their conclusions. To do so, it is helpful to develop and to summarize in outline form the generalizations concerning mechanism and configuration which have fewest exceptions:

1. Step 1. *A salt-like complex is first formed between the oxime and the rearrangement agent, usually an exothermic reaction.* So much heat is occasionally evolved that it is sometimes mistaken by investigators for the rearrangement proper. It can be demonstrated in most cases that the step is reversible by aqueous decomposition of the complex to the original oxime.

2. Step 2. *An ester (or picryl ether) grouping of a type that is potentially capable of ionization is next formed from the complex by elimination of water or of some other simple molecule.* The majority of cases, particularly with phosphorus pentachloride as an agent, comply with this generalization, though exceptions can be found. For example, Lachmann's rearrangement of benzophenoxime in aqueous hydrochloric acid (5) is difficult to imagine as proceeding through an ester formation step. Yet, Chapman (6) presents evidence that an ester-like compound may form under these circumstances from the reaction of the oxime and N-phenylbenzimidyl chloride, the latter arising from the action of hydrochloric acid on benzanilide. It is at least noteworthy that all *effective* agents for the rearrangement are electrophilic in nature and capable of forming esters with the oxime.

It is emphasized that the following generalizations refer to a single step (3A) and are made separable only for the sake of describing the dual nature of the forces within the molecule which affect rearrangement.

3. Step 3A. *The ease of ionization of the ester partly determines the rate and/or*

ease of rearrangement.[1] As one of many illustrations, Kuhara (1) has shown that the acetate esters of oximes rearrange more slowly than chloroacetate esters which, in turn, rearrange more slowly than benzenesulfonic esters. Also, it is well known that the rearrangement rate is increased by choice of a solvent of high dielectric constant, which would favor ionization.

4. Step 3A. *The rate and/or ease of rearrangement partly depends on the relative tendency of the migrating group to donate a pair of electrons to the nitrogen atom by migration of the entire group* (*3*, *4*, *9*). Generalizations 3 and 4 are, therefore, visualized as a "push and pull" process entirely analogous to Bartlett's theory as applied to the pinacol rearrangement (7). The ionization of the ester is considered to be the "pull" and the migration tendency of the migrating group to be the "push". Chapman (3, 4) has further shown that the *non-migrating group* has the same relative tendency to influence migration rates but to a much lesser extent. The above generalizations permit no explanation of the latter phenomenon. A possible explanation is made later at a more appropriate place in the discussion. Generalization 4 is confirmed by the following supplementary statements:

a. *The migrating group which attaches itself to the nitrogen atom is anti to the hydroxyl group in the original oxime.* Though anti attachment of groups was surprising to early workers, it is now considered to be a normal attachment from consideration of the mechanism of many other reactions. Certainly, it is an essential feature of Bartlett's "push and pull" theory (7).

b. *The migration of the alkyl or aryl group takes place intramolecularly.* This is another confirmation of the inseparable nature of generalizations 3 and 4, and its truth has been amply demonstrated by Campbell and Kenyon (8).

The generalizations are illustrated by the following equations using the oximes and conditions pertinent to the experimental work:

$$\underset{\substack{\text{Ia R = H}\\ \text{Ib R = CH}_3\\ \text{Ic R = Cl}}}{\mathrm{RC_6H_4\overset{\overset{\textstyle NOH}{\|}}{C}{-}CH_3}} + \mathrm{H_2SO_4} \underset{\text{Rapid, exothermic}}{\xrightleftharpoons{\text{Step 1}}} \underset{\substack{\text{II}\\ \text{Oxime Salt}}}{\mathrm{RC_6H_4\overset{\overset{\textstyle NHOH^+}{\|}}{C}{-}CH_3}} + \mathrm{HSO_4^-}$$

$$\underset{\text{Presumably rapid}}{\xrightleftharpoons[-\mathrm{H_2O}]{\text{Step 2}}} \underset{\text{III}}{\mathrm{RC_6H_4\overset{\overset{\textstyle NOSO_2OH}{\|}}{C}{-}CH_3}} \underset{\text{Rate-determining}}{\xrightarrow{\text{Step 3A}}} \left[\begin{array}{l}\mathrm{RC_6H_4N}\\ \qquad\quad \|\\ \qquad\ \mathrm{{}_{+}CCH_3}\end{array}\right] + \mathrm{HSO_4^-}$$

$$\underset{\text{Very rapid}}{\xrightarrow{\text{Step 3B}}} \underset{\substack{\text{IV}\\ \text{Imidyl Sulfate}}}{\mathrm{HO_3SO\overset{\overset{\textstyle RC_6H_4N}{\|}}{C}{-}CH_3}} \xrightarrow{\mathrm{H_2O}} \mathrm{RC_6H_4NH\overset{\overset{\textstyle O}{\|}}{C}CH_3} + \mathrm{H_2SO_4}$$

[1] The rate comparison is obvious, and the ease of rearrangement is correlated arbitrarily with the heat of activation.

The ion is bracketed in Step 3A to show its momentary, fleeting existence. However, the imidyl sulfate existence is definitely real, as Coleman and Pyle (10) have utilized similar products of the Beckmann rearrangement in the preparation of other compounds.

DEVELOPMENT OF METHODS OF ANALYSIS FOR RATE STUDIES

To study the above reactions it was essential to develop a method of analysis for accurate determination of either the oxime or the amide in the presence of one another and in the presence of sulfuric acid. Sluiter (11) had previously measured the rate of rearrangement of acetophenoxime by determining the amount of acetic acid from the hydrolyzed amide. But, in the hands of the Vanderbilt investigators, it yielded erratic results even with obvious improvements; the average yield was 95% ± 4% for 22 samples. The 2,4-dinitrophenylhydrazine analysis of Iddles (12) was next tried and proved to be satisfactory for the determination of acetophenoxime (99.2% ± 2%) and less so for the *p*-chloro derivative (98% ± 2.5%) and the *p*-methyl derivative (95% ± 4%). The higher the melting point of the hydrazone the more accurate were the results. Details of the method are given in the experimental. After accumulating considerable data in this manner, the method was finally abandoned for one of more accuracy, greater ease of manipulation and of wider scope. It consisted of oxidizing the oxime with ferric sulfate and titrating the ferrous sulfate with potassium dichromate, a procedure adapted from the paper of Bray, Simpson, and MacKenzie (13). Even with this method, difficulties were encountered, as aromatic amides (but not aliphatic amides) underwent slight but noticeable oxidation by ferric sulfate. Correction curves were, therefore, necessary. The accuracy can best be judged by the "pseudo runs" shown in the experimental.

PRESENTATION OF RESULTS

The rearrangements followed first order rate curves corroborating results of Sluiter. Sluiter's work, in addition, has shown that the first-order rate constant in excess sulfuric acid remained unchanged over an appreciable range of oxime concentration. Accordingly, all runs in this paper were made *approximately* at one concentration. The experimental results of the oxidation method are presented in Table I and compared with the results of the dinitrophenylhydrazone method and Sluiter's data in Table II.

A comparison of Table I and Table II shows that the results do not agree well enough to draw absolute conclusions about the rate constants, activation energies or entropies. Table I is perhaps nearest the truth, but both tables are considered relatively accurate enough for qualitative conclusions to be drawn. In Figure 1, the logs of the rate constants are plotted against reciprocal temperatures to illustrate the validity of application of the Arrhenius equation to the rearrangement reaction.

DISCUSSION OF RESULTS

It is evident from Table I that Chapman's results have been substantiated as given in Generalization 4. The rates of rearrangements were found to be in the

TABLE I

RATE CHARACTERISTICS OF THE REARRANGEMENT OF ACETOPHENONE OXIMES IN SULFURIC ACID (OXIDATION METHOD)[a]

OXIME $RC_6H_4C(=NOH)CH_3$	T°C	k[b]	HALF-LIFE[c]	E_A[d]	ΔS[e]
R = H	50.9	0.0011	630		
	60.9	.0036	190	24	−8
	64.9	.0053	130		
R = CH_3	40.9	.0004 (3)	1600		
	50.9	.0021	330	24.5	−5
	55.9	.0039	180		
R = Cl	50.9	.0007	990		
	55.9	.0012	580	22.5	−14
	60.9	.0022	310		

[a] All rates run with approximately 0.0226 mole of oxime in 25 cc. of 95.5% H_2SO_4.

[b] $k = \frac{2.303}{t} \times \log \frac{a}{a - x}$; reciprocal minutes.

[c] $t_{1/2} = \frac{0.693}{k}$; minutes.

[d] $\log k_2/k_1 = \frac{E_A}{2.303R} \times \frac{T_2 - T_1}{T_2T_1}$; kilocalories.

[e] $k = \frac{KT}{h}(e^{\Delta S/R})(e^{-E_A/RT})$; entropy units.

TABLE II

RATE CHARACTERISTICS DATA FROM SLUITER AND FROM 2,4-DINITROPHENYLHYDRAZONE METHOD

OXIME	CONC. OF H_2SO_4	T°C	k	HALF-LIFE (MINUTES)	E_A	METHOD
R = H	93.5	61	0.0023	300		DNPH[a]
	96.0	61	.0027	250		
	96.0	71	.0083	85	25.5	
	100.0	61	.0040	170		
R = H[b]	93.6	65	.0019	160		Sluiter
[c]	93.6	65	.0019	160		
[c]	93.6	60	.0011	275	24.5[d]	
[c]	97.2	60	.004	75		
R = CH_3	96.0	51	.0019	360		DNPH
	96.0	61	.0065	110	26.5	
R = Cl	96.0	61	.0020	350		
	96.0	71	.0060	110	25.5	
R = H	96.0	61	.0042	170		
Oxime Acetate	96.0	71	.0136	50	26.5	

[a] DNPH—Dinitrophenylhydrazone method. Concentration same as Table I, unless designated as *b* or *c*.

[b] Conc.: 2.5 g. Oxime/100 cc. H_2SO_4.

[c] Conc.: 2.5 g. Oxime/50 cc. H_2SO_4.

[d] Calc'd in this laboratory.

order: *p*-methyl derivative (Ib) > acetophenoxime (Ia) > *p*-chloro derivative (Ic). In a practical sense, therefore, the results have been quite satisfactory. A general idea of the conditions and times for complete rearrangement can be obtained by reference to the tables. Also, if electronic interpretations continue

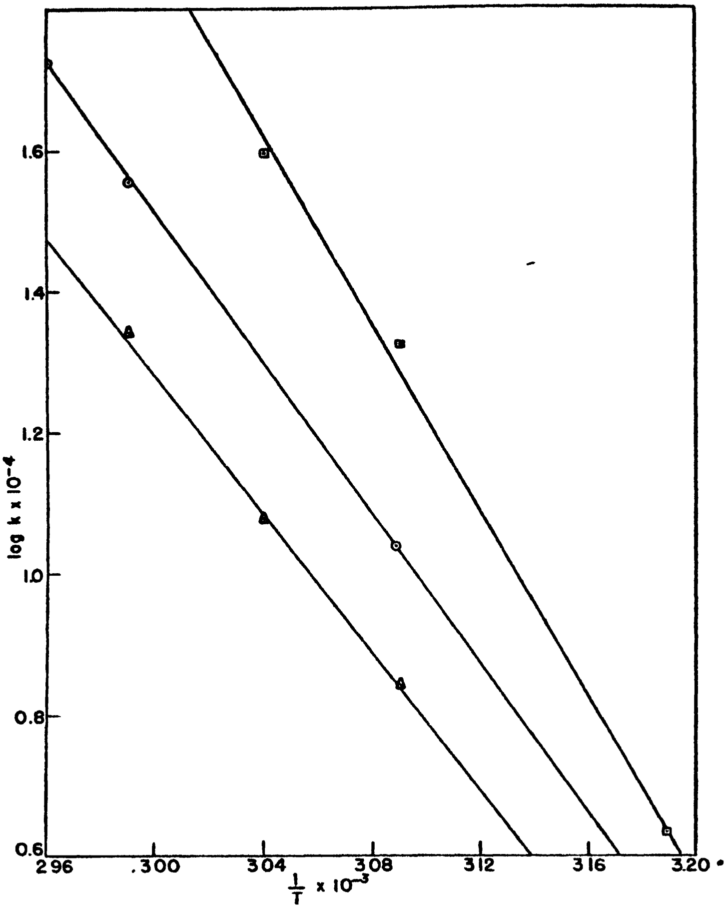

FIGURE 1

BECKMAN REARRANGEMENT OF ACETOPHENONE OXIMES $(RC_6H_4C{-}\overset{\overset{NOH}{\|}}{C}CH_3)$
LOG OF THE RATE CONSTANTS VERSUS RECIPROCAL TEMPERATURES
⊙ R = H; ⊡ R = CH_3; △ R = Cl

to hold, some qualitative predictions may be made as to other oxime rearrangement rates. Aliphatic oximes should rearrange more slowly than aromatic-aliphatic oximes, and aromatic oximes should rearrange slightly faster than the aromatic-aliphatic oximes. If electronegative groups are attached to the migrating or non-migrating group, the rates should be slower or slightly slower

respectively. Exceptions will possibly be found in later work as the entropy terms (ΔS) are not constant. In fact, the rearrangement is so intricate, considering complex formation, reagent characteristics, and consequences of consecutive reactions, that it is perhaps fortunate that the rate sequence was in the order predicted from the generalizations. With acetophenoxime, the situation was further complicated by sulfonation, contrary to textbook statements (14). Such complications were reflected in the activation energies and entropy terms, which could not be resolved into simple, qualitative relationships. For that matter, Chapman's activation energies and entropy terms (the latter calculated in this laboratory) were as difficult to analyze.

An interesting aspect of Table II results is the great dependence of the rates of reaction on sulfuric acid concentration. Hammett and Deyrup (15) explain this phenomenon as due to the "hyperacidity" of the sulfuric acid and show that the rates parallel the acidity function, H_0 (16). Their explanation would hold as well if it is considered that the esterification rate (Step 2) is dependent on the sulfuric acid concentration. *This would mean that sulfate formation (Step 2) was the rate determining step of the rearrangement and that all above predictions on rates of rearrangement in sulfuric acid applied to the esterification reaction.* The slightly greater activation energy of acetophenoxime acetate as compared to the oxime itself (comparison by Table II only) might be interpreted in this light as a slight blocking of sulfate formation by the acetate radical. The assumption was at least worthy of consideration, and efforts were made in the next part of this paper to isolate the acetophenoxime-O-sulfonic acids (IIIa, b, and c), possible intermediates in the rearrangements of the oxime in sulfuric acid, and to investigate their behavior.

ISOLATION AND CHARACTERISTICS OF THE ACETOPHENOXIME-O-SULFONIC ACIDS

Sanford, Sherk, *et al.* (17) have described the formation of acetanilide from the exothermic reaction of acetophenone and hydroxylamine-O-sulfonic acid but stated that the sulfonic ester was probably not an intermediate. Smith (18) described the preparation of the potassium salt of acetophenoxime-O-sulfonic acid and its rearrangement to acetanilide by 4 *N* HCl in dioxane. It thus appeared possible to isolate acetophenoxime-O-sulfonic acid and its *p*-substituted derivatives. After numerous trials, it was found that the simple addition of the oxime to chlorosulfonic acid in ether solution precipitated the desired acid. The study of these acids, (IIIa, b, and c), however, was another matter, as they were hygroscopic, unstable, and easily hydrolyzed to the oxime salts (IIa, b, and c). A more complete description is given of the most tractable acid, the *p*-methylacetophenoxime-O-sulfonic acid. It was a white, free-flowing powder (acid equiv. calc'd: 229; found: 219.5) which decomposed abruptly when heated on a spatula, when touched with a hot wire, or when immersed in a bath at 80° (flashes at 84° and resolidifies). When suspended in ethylene chloride, it was converted *exothermically* at about 45° into at least 80% *p*-methylacetanilide. If placed in a loosely stoppered weighing bottle, it was slowly hydrolyzed to the oxime salt (IIb) (acid equiv. calc'd: 123.5; found: 127.5), which did not rearrange

in refluxing ethylene chloride; rather, a 91% yield of oxime was obtained. The other oxime acids behaved similarly. The *p*-chloro derivative (IIIc) gave a better acid equivalent but was more hygroscopic. The acetophenoxime-O-sulfonic acid (IIIa) was so reactive that the removal of the last trace of solvent at room temperature brought about spontaneous decomposition, unless special precautions were taken.

The above description implies that the acetophenoxime-O-sulfonic acids are so reactive that they undoubtedly rearrange spontaneously in sulfuric acid at the temperature of rearrangement *provided they are intermediates*. The rate-determining step would, therefore, be the oxime-O-sulfonic acid formation (Step 2) an assumption which would alter general concepts of the rearrangement. It would mean that the correlation of group tendency to migrate (considered as a part of the rate-determining step) has been communicated to the oxime hydroxyl group by controlling the rate of esterification——perhaps as simple a matter as an increase or decrease of acidity of the oxime hydroxyl group. The influence of the *non-migrating* aryl or alkyl group on reaction rates would thus be explained, since it, too, would affect the acidity of the oxime.

However, the actual behavior of the acetophenoxime-O-sulfonic acids in sulfuric acid cast some doubt on belief that they were intermediates. At low temperature, they were converted to the oxime salt (II), illustrating the reversibility of Step 1, and at high temperature they underwent almost an explosive decomposition, giving serious side-reactions. At intermediate temperatures, they were partly converted to amides in yields greater than estimated from the reaction rate constant. However, this may have been due to local heating effects, as considerable heat was evolved in introducing the oxime esters into sulfuric acid. The question will best be decided by other experimental means with more workable intermediates.

Whether the oxime-O-sulfonic acids are intermediates or not, the spontaneity of their rearrangement suggests that either ester formation (Step 2) is the rate-determining step, or one of lower activation energy level than ester formation. The only likely possibility is the elimination of water from the oxime salt, as postulated by Lachmann (5):

$$\overset{\displaystyle NHOH^+}{\overset{\|}{RC_6H_4CCH_3}} \quad HSO_4^- \xrightarrow[\text{Possibly rate-determining}]{-H_2O} \left[\overset{\displaystyle N}{\overset{\|}{RC_6H_4CCH_3}}\right]^+ HSO_4^-$$

The latter step still indicates that the rearrangement tendencies of oximes in sulfuric acid are determined by an earlier step than the actual rearrangement (Step 3A). In other words, the actual migration of the aryl group or alkyl group of the oxime in sulfuric acid appears to be an extremely rapid and exothermic reaction. It is, therefore, interesting to note that Chapman's work, involving the rearrangement of picryl ethers of the oximes in polar organic solvents, and the work of this paper, involving sulfuric acid rearrangement, have different rate-determining steps and yet yield qualitatively the same rate sequences and the same approximate energy requirements. It could be best explained, in the

opinion of the authors, on the basis of the parallelism of migration tendencies and of other chemical functions of the oximes.

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EXPERIMENTAL

Part I. Reaction Rate Measurements

A. *Oxime purifications.* The oximes were prepared by standard methods, recrystallized at least once from methyl alcohol and finally from cyclohexane. Acetophenoxime (Ia), m.p. 57.5–57.8°; acetophenoxime acetate, m.p. 55–56°, mixed m.p. with I: below room temperature; *p*-chloro oxime (Ic), m.p. 97.5–98°; p-methyl oxime (Ib) m.p. 87–88°. All of the oximes were stored in evacuated desiccators over soda lime.

B. *Development of oxime determinations.* 1. *The acetic acid method.* Sluiter's procedure (11) was rejected on first trial as the distillate gave positive sulfate tests. The following modifications helped: a series of accurately weighed acetanilide samples from 0.05 g. to 0.2 g. was dissolved separately in 20 cc. of water and 1 cc. of concentrated sulfuric acid contained in a 50 cc. distilling flask with condenser. The sulfuric acid was neutralized with 0.5 N alkali to methyl orange end-point and made slightly acid again with dilute sulfuric acid. In this manner the sulfuric acid was converted to sodium acid sulfate. The solution was distilled until no more vapor could be forced over. Since bumping was a serious problem, the distillate was redistilled. The condensers were washed after each distillation and added to the distillate. The distillate was then titrated with 0.1 N sodium hydroxide to phenolphthalein end-point. Twenty-two samples gave yields of 95% acetic acid ± 4%. No further work was done by this method.

2. *The 2,4-dinitrophenylhydrazine method* (12). Samples of oxime, varying in weight from 0.05 g. to 0.2 g. were individually suspended in 15 cc. of water, and one cubic centimeter of concentrated sulfuric acid and an amount of 2,4-dinitrophenylhydrazine equivalent to 100% excess were added to the suspension. The initial samples, containing large amounts of oxime, usually required about 0.3 g. of hydrazine and, as the oxime concentration became smaller, about 0.1 g. A constant amount of 2,4-dinitrophenylhydrazine made no difference in the gravimetric procedures, but the washings of the precipitate were more difficult with the smaller samples of oxime. The hydrazone formed a yellow, flocculent precipitate immediately, but the mixture was heated on a steam-bath to ensure complete reaction. The samples were then cooled and diluted to approximately 450 cc. The hydrazone, either before or after dilution could not be allowed to stand overnight as the excess 2,4-dinitrophenylhydrazine in dilute sulfuric acid formed a bright, red compound which could not be washed out. The dilution was essential as the hydrazone was somewhat soluble in more concentrated solutions of acid. Furthermore, the filtrations were easier after dilution due to the character of the precipitate. The precipitate was then filtered through Gooch crucibles with asbestos, washed with 125 cc. of 2 N HCl and with about 400 cc. of hot water until the filtrate was colorless. The crucibles were dried at 100–105° overnight or to constant weight. Acetophenone-2,4-dinitrophenylhydrazone yields: 99.2% ± 2%, 15 samples; *p*-chloro derivative 98% ± 2.5%, 8 samples; *p*-methyl derivative 98% ± 3% at 0.1 g. oxime concentration and 92.5% ± 3% at 0.05 g. oxime concentration, 20 samples. The analysis of the *p*-methyl derivative was improved somewhat by adding 2 cc. of concentrated ammonium hydroxide before addition of 2,4-dinitrophenylhydrazine.

3. *The oxidation method* (13). The analyses were made comparable to actual runs. Accurately weighed mixtures of the oximes and the rearrangement product (usually the amide but, in the case of acetophenoxime, sulfanilic acid) were suspended in 25 cc. of water contained in a 150-ml. beaker covered with a watch glass. After the addition of 1 cc. of concentrated sulfuric acid, the suspension was heated and held near the boiling point for

5–10 min. or until the crystalline oxime became oily. The samples were then removed from the hot plate, the sides of the beaker and the watch glass washed with a stream of distilled water and 0.8 g. of ferric sulfate added. Again the samples were heated and boiled gently for 5 min. After removing from the hot plate, the sides of the beaker were again washed and 5 cc. of benzene added to prevent oxidation of the ferrous sulfate while cooling in an ice-bath. Phosphoric acid (50%, 10 cc.) and 6 drops of sodium diphenylaminesulfonate

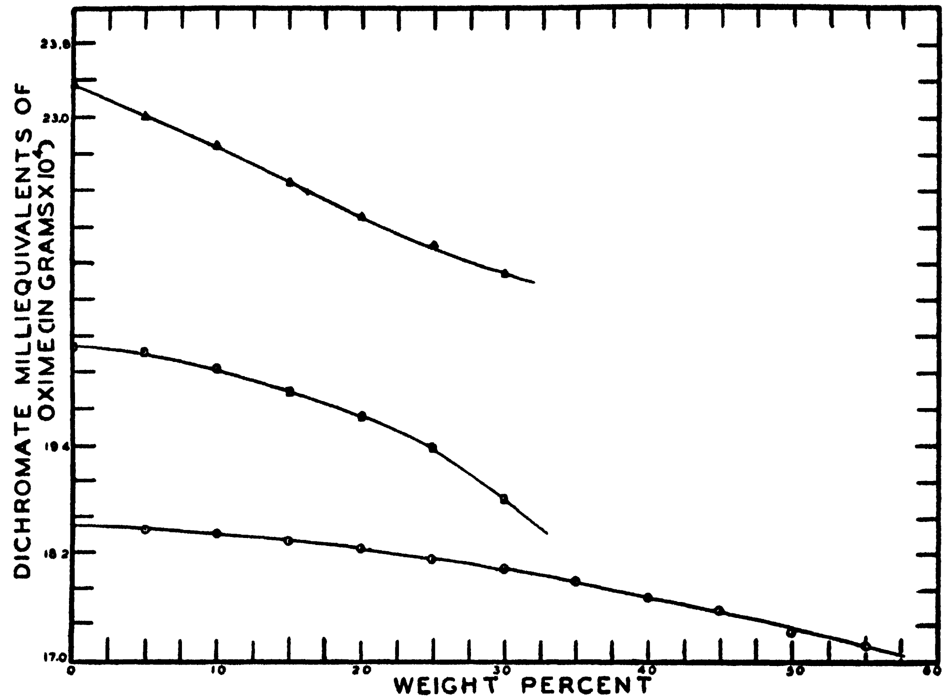

FIGURE 2

DETERMINATION OF ACETOPHENONE OXIMES ($RC_6H_4C(=NOH)-CH_3$) IN PRESENCE OF REARRANGED PRODUCT (OXIDATION METHOD)

Dichromate milliequivalent of oxime versus weight per cent of rearranged product[a].

⊙ R = H and Sulfanilic Acid

⊡ R = CH_3 and p-Methylacetanilide

△ R = Cl and p-Chloroacetanilide

[a] Points are composites of at least 4 determinations for each point.

solution (19) were added, and the samples immediately titrated with 0.027 *N* potassium dichromate. Approach of the end point is indicated by the appearance of a bright green color which is changed by the addition of one more drop to a purple color. The presence of the rearrangement product had a noticeable but reproducible effect on the milliequivalence of the dichromate as indicated in Figure 2.

Since the correction factor was appreciable above 40% rearranged product, no runs were sampled beyond this limit. In calculating unknown oxime concentrations, a method of approximation was used as follows: the original weight of oxime with zero per cent rearranged product was known and required Y cc. of dichromate. The unknown sample re-

quired X cc. to titrate. Therefore, X/Y gave the per cent rearranged product from which the approximate milliequivalence of the dichromate solution could be selected from the curve (Fig. 2). After calculation of the concentration of the oxime, this figure, a more accurate one, was used to calculate X/Y again, from which the correct milliequivalence of the dichromate solution could be selected. Pseudo runs were made to check the accuracy of the method whereby mixtures of oxime and rearranged product were weighed out by the senior author and titrated by the junior author. The results are given in Table III.

TABLE III

PSEUDO RUNS FOR DETERMINATION OF OXIME CONCENTRATIONS IN PRESENCE OF REARRANGED PRODUCTS (OXIDATION METHOD)

$RC_6H_4C(=NOH)CH_3$	WEIGHT PERCENT REARRANGED PRODUCT	WEIGHT OF OXIME	WEIGHT OF OXIME CALC'D
R = H	Sulfanilic Acid		
	0	0.0752 g.	0.0750 g.
	8.35	.0700	.0696
	16.4	.0652	.0658
	24.2	.0602	.0602
	31.8	.0550	.0551
	39.2	.0503	.0501
R = CH_3	*p*-Methylacetanilide		
	0		
	3.3	0.0725	0.0730
	6.8	.0699	.0687
	10.0	.0675	.0667
	13.5	.0649	.0653
	20.0	.0600	.0590
	26.2	.0554	.0563
R = Cl	*p*-Chloroacetanilide		
	0		
	11.4	0.0797	0.0805
	20.0	.0751	.0760
	25.0	.0675	.0706
	30.2	.0628	.0647
	25.0	.0674	.0698
	22.0	.0703	.0690

C. *Rate determinations.* Approximately 0.0226 mole of oxime was weighed accurately and placed in a test-tube, 17 x 2.5 cm., with a ground-glass stopper. Sulfuric acid (25 cc., Merck, C.P.) was pipetted into a tared, dry flask, weighed, then poured into the test-tube which contained the oxime. The flask was reweighed to obtain the weight of sulfuric acid to 0.01 g. With acetophenoxime and the *p*-methyl derivative, it was necessary to cool the test-tube. When the oxime had dissolved, the test-tube was immersed immediately in a constant temperature bath and the temperature was maintained at ±0.02°. At various intervals aliquots were removed with a 1-cc. pipette and the amount of sulfuric acid delivered determined by weighing the pipette before and after delivery of the sulfuric acid solution to a 150-cc. beaker containing 25 cc. of water. The aliquots were then treated exactly as shown in B-3. The weight of oxime found was then converted by the aliquot factor to weight of oxime left in original sample, which figures are given in Table IV.

TABLE IV

RATE DATA OF ACETOPHENONE OXIMES. TIME IN HOURS; WEIGHT IN MILLIGRAMS OF OXIME

$RC_6H_4C(=NOH)-CH_3$ T°C	0	0.5	1.0	1.5	2	3	4	6	8	10
PART A—OXIDATION METHOD										
R = H										
50.9	64.5		60.4		56.9		49.8	43.2	38.5	35.5
	64.7		61.2		56.5		50.3	43.0	39.6	36.3
60.9	62.8			47.3	39.9	32.7	28.7			
	61.9		50.7		41.0					
64.9	62.5	53.5	44.1	35.0	32.7					
	61.6	52.5	43.3	35.4	28.8					
R = CH_3										
40.9	69.1		67.4			63.8	61.2[c]	58.5[2b]		
			66.9		65.7		63.8	58.1		53.5[-c]
50.9		68.0	64.0	58.2		53.1				
	72.2	69.1	63.3	59.7	55.0					
55.9	67.6	61.8		48.8	43.3					
		61.9	47.7							
R = Cl										
50.9	82.5		79.8		71.2[b]		68.1	64.5		
	81.0		78.7		70.3[b]		70.1	62.3[a]	56.9[c]	
55.9	77.0		70.5	69.3[a]	64.9[b]	60.8[b]	55.8[a]			
60.9	78.8	70.7	67.0	59.7[a]	54.5[c]					
	77.8	75.2	68.6	62.2[a]	55.3[c]					
PART B—DNPH METHOD										
R = H										
61.0[d]	64.8		55.4[a]			43.4		32.4[b]		17.5
61.0[e]	59.1	53.4	47.0			27.9		10.5	4.6[2b]	
61.0[f]		59.5	47.7		45.9		31.0			10.2
71.0	61.6	49.0		26.5	15.1[b]		9.7	2.6		
Acetate										
61.0	91.2	78.3		62.4			34.3			
71.0	90.3	58.6	40.4		13.4[b]		4.7			
R = CH_3										
51.0	74.8		69.7			55.1				24.4
61.0	76.6	63.8	50.8			23.9				
R = Cl										
51.0	81.4		76.2			55.9[a]		39.8		28.0
71.0		62.7			35.5	26.4	11.3[2b]			

[a] = +0.25 hours; [b] = +0.5 hours; [c] = +0.75 hours. [d] = 93.6% H_2SO_4; [e] = 100% H_2SO_4; [f] = 96% for this and all other DNPH runs. The oxidation runs were with 95.5% H_2SO_4.

PART II

A. *Preparation of acetophenoxime-O-sulfonic acids (III a, b, and c).* To a solution of 0.06 mole of chlorosulfonic acid (b.p. 147–150°/748) in 75 cc. of ether (dried over P_2O_5) in a three-necked flask protected with a calcium chloride tube was added dropwise a solution of 0.05 mole of oxime in 75 cc. of dry ether while stirring and cooling in an ice-bath. The oxime-O-sulfonic acid had finished separating after half an hour, and was filtered with slight suction and washed by successive resuspensions with a total of 500 cc. of dry ether in such a way that the solid was never allowed to become completely dry. It was then sucked dry for 5–10 seconds and immediately dried *in vacuo* over P_2O_5. The efficiency with which the products were protected from moisture during these operations determined the purity of the oxime-O-sulfonic acids, which were all white, free-flowing powders. The yields were: IIIa, 70%; IIIb, 75%; IIIc, 50%.

B. *Reactions of p-methylacetophenoxime-O-sulfonic acid (IIIb).* IIIb was the most stable of the acids; its m.p. was 84°, instantaneous decomposition when placed in bath at 80° otherwise 132–145°. Its acid equiv. by glass electrode titration was 204, 219.5 (two runs); calc'd; 229; undoubtedly, some hydrolysis had taken place during titration. IIIb was halogen-free by silver nitrate test. If exposed directly to air, IIIb deliquesced, but, if partly exposed, such as in a loosely-stoppered weighing bottle, its neutral equiv. changed in a period of 2 days to 126.8, 127.5 (calc'd for oxime salt, IIb: 123.5).

Rearrangement: IIIb (acid equiv.: 204, 0.012 mole) was suspended in 30 cc. of ethylene chloride and heated to 47° whereupon a spontaneous rearrangement began, which maintained itself at this temperature for 4 minutes. The solid was filtered (m.p. 147–153°), washed thoroughly with sodium bicarbonate solution and dried. Yield: 80% *p*-methylacetanilide; m.p. 144–148.5°; recrystallized from alcohol, m.p. 149–150.5°; mixed m.p. with authentic sample 149–151°. Attempted rearrangement of IIb (acid equiv.: 127.5) under the same conditions, except that the ethylene chloride suspension was refluxed, yielded 91% *p*-methylacetophenoxime, m.p. 81–87°, recrystallized from alcohol m.p. 86–88°; mixed m.p. with authentic sample 86–88°. Attempts to run an aqueous rearrangement of IIIb failed; only *p*-methylacetophenone was obtained.

Reaction with concentrated H_2SO_4: IIIb (1 g.) was carefully dissolved in 6 cc. of mechanically stirred 96% sulfuric acid maintained at 32–33°. After 10 min. the mixture was poured on ice, neutralized with sodium hydroxide, and allowed to cool overnight. The yield was 0.55 g. (85%) of crude *p*-methylacetophenoxime, m.p. 79–81°, recrystallized from cyclohexane, m.p. 85–87°. Similarly, IIIb, dissolved in H_2SO_4 at 43–45°, yielded 84% of a mixture of oxime and *p*-methylacetanilide of which at least 50% was the amide (separated by cyclohexane). More amide is thus formed than expected from rearrangement of the oxime. However, local heating effects were noticeable especially if IIIb was introduced into the sulfuric acid in portions larger than 0.1 g.

C. *Reactions of acetophenoxime-O-sulfonic acid (IIIa).* IIIa was the most reactive of the acids; it could only be dried in a desiccator with P_2O_5 by cooling desiccator to ice temperature before evacuation. IIIa melted at 80°, instantaneous decomposition if placed in bath at 78°. Its acid equiv. was 202; calc'd: 215. The oxime salt (IIa) was an oil.

Rearrangement: IIIa (0.012 mole) was suspended in 30 cc. of ethylene chloride. A spontaneous reaction began at 40° and maintained itself (with external cooling), at 40–45° for 10 minutes. After washing with bicarbonate solution, a 70% yield of acetanilide was obtained, m.p. 101–109°, recrystallized from cyclohexane m.p. 114–115°. The method was quite adaptable to large scale preparations of amides by the Beckmann rearrangement: the oxime (0.06 mole) was added to chlorosulfonic acid (0.075 mole) dissolved in 100 cc. of ethylene chloride. The flask was heated cautiously to the point where the internal temperature exceeded the external one by a few degrees. Cooling was sometimes necessary. After the usual purification, a yield of approximately 0.05 mole of amide was obtained.

Hydrolysis: IIIa (1 g.) was dissolved in 96% sulfuric acid which was well stirred and maintained at 23–25° during addition. After 10 minutes reaction, the mixture was poured on to ice and neutralized with NaOH solution. An 80% yield of acetophenoxime was ob-

tained. Similarly, IIIa in H_2SO_4 at 45–46° for 10 minutes yielded 83% acetophenoxime and no amide. Rather than continue this study with an unstable acid, it was instead converted to the potassium salt by neutralization with aqueous $KHCO_3$. This product and the one obtained by the method of Smith (18) were identical (m.p. 210–211°, dec., considerable previous sintering; m.p. 152° with resolidification when placed in a bath at 150°; the latter m.p. was erratic but was always sharp).[2] The potassium salt (2 g.) was dissolved in 10 cc. of H_2SO_4 under conditions given below and yields of oxime or amide found.

H_2SO_4, %	T°C	TIME	% OXIME	% AMIDE
		min.		
96	10.0	12	83	0
96	25–30	7	65	5
96	40–45	9	47	28
100	26–28	4	91.5	0

D. *Reactions of p-chloroacetophenoxime-O-sulfonic acid (IIIc).* IIIc was most hygroscopic of the acids. Its m.p. was 87.5°, dec. when placed in bath at 80°. Its acid equiv. was 239.5, 239.5; calc'd: 249.5.

Rearrangement: IIIc (0.016 mole) was suspended in 30 cc. of ethylene chloride. Spontaneous rearrangement did not begin till 56°, whereupon the temperature rapidly rose to 62–63° and maintained itself for 2 minutes. During this time, the solid changed to an oil. After treatment with bicarbonate solution and the usual purification, *p*-chloroacetanilide (m.p. 178.5–180°, mixed m.p. with authentic sample 179–181°) was obtained in 84.5% yield. IIIc was also hydrolyzed to *p*-methylacetophenoxime in 85% yield by dissolving in water and allowing it to stand for several days (m.p. 83–94°; recrystallized from cyclohexane, m.p. 97–98°).

SUMMARY

Some generalizations on the mechanism of the Beckmann rearrangement have been summarized. A method of analysis of the oxime in the presence of its rearrangement product has been developed to facilitate kinetic studies of the rearrangement of oximes in sulfuric acid. The results confirmed the generality that alkyl substituted acetophenone oximes rearrange faster than acetophenoxime which, in turn, rearranges faster than electronegatively-substituted acetophenone oximes. The possibility of ester formation as an intermediate in the rearrangement has been studied by synthesis and characterization of the acetophenoxime-O-sulfonic acids. Their properties suggest that the rate-determining step is either ester formation or a similar step involving a lower activation energy level than that of ester formation, such as loss of water from the oxime salt. It is not possible from the experimental evidence to decide which of these steps was the truth. In any event, the rate of formation of rearranged product is determined by either one or both of these steps and not by the actual migration of the aryl or alkyl group.

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[2] The difficult recrystallizations of the potassium salt by Smith (18) were unnecessary, as it could be suspended in boiling alcohol and triturated with water until dissolved, filtered while hot, and then cooled. The salt crystallized with 0.5 mole of water which was removed in Abderhalden dryer at 100° and at low pressure. Calc'd for $C_8H_8NO_4SK$: C, 37.9; H, 3.16; S, 12.63. Found: C, 37.77; H, 3.36; S, 13.0. The drying process raised the m.p. 152° when placed in a bath at 150° to approximately 192° (sudden immersion).

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BRANCHED-CHAIN FATTY ACIDS. VIII. SYNTHESIS OF TWO ACIDS CONTAINING A 3-PENTYL SYMMETRICAL END-GROUPING

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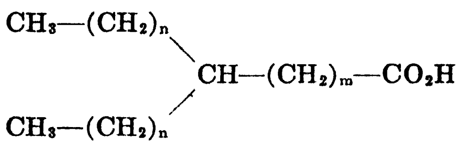
In a previous publication (1), in which there was discussed the relationship of melting point to structure of branched-chain acids, it was shown that the iso acid is the only known type of high molecular weight branched-chain acid which has a melting point less than ten degrees below the melting point of the normal acid, with the same number of carbon atoms. Since the high melting point of the iso acid might be attributable to the symmetrical end-group, we have investigated this point by synthesis of acids with a structure such as indicated in formula I.



I

II n = 1, m = 12

III n = 1, m = 13

In the present paper is reported the synthesis of two such acids, 14-ethylhexadecanoic acid (II) and 15-ethylheptadecanoic acid (III). Each of these acids, whose branching end-groups are ethyl, has a melting point far below that of the normal isomer. The C_{18} acid (II) melts at 42.0–42.9°, and the C_{19} acid (III) melts at 36.7–37.4°. Thus, the latter melts even lower than 16-methyloctadecanoic acid, m.p. 49.9–50.6° (2), which has the same molecular weight and a methyl group in the same position relative to the end of the chain. It is also of interest that the C_{18} acid (II), which has an even-carbon straight chain, melts 5.5° above the C_{19} acid (III), which has an odd-carbon straight chain. This is reasonable, in view of the known relationship between the melting points of normal acids with odd- and even-carbon chains; however, this relationship does not hold for the iso acids. An even-carbon iso acid (3), which has an odd-carbon straight chain, melts at nearly the same place as the normal acid with the same number of carbon atoms, therefore higher than the odd-carbon normal acid corresponding to the straight chain in the iso acid.

Thus, the high melting points of iso acids must be attributed to some factor other than the symmetrical end-grouping. Velick's study (4) of the X-ray diffraction patterns exhibited by iso acids appears to offer a reasonable explanation[3] of the remarkably high melting points exhibited by the iso acids. The

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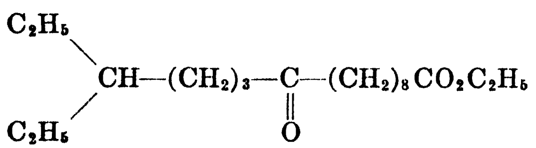
[3] This interpretation was suggested to the authors in a private communication from Dr. A. W. Weitkamp of the Standard Oil Company of Indiana, Whiting, Indiana.

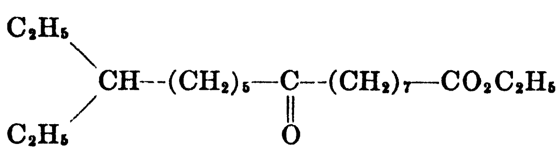
crystal structures of the iso acids appear to be similar to those of the normal acids except for a large angle of tilt of the axis of the acid chain relative to the planes between the layers. This tilting may permit accommodation in the crystal lattice of the branching group, provided that the branching group is at the end of the chain and no larger than methyl. When the branching group is larger or not at the end of the chain, such a crystal structure is not possible, hence other crystal structures resulting in lower melting points are adopted.

The melting-point pattern exhibited by acids with symmetrical end-groups larger than ethyl is reported in the following paper of this series.

The starting material for synthesis of acids, II and III, was 2-ethyl-1-butanol. For synthesis of 14-ethylhexadecanoic acid (II), the chain of this alcohol was extended by means of the Grignard reaction with ethylene oxide, and ethyl 10-keto-14-ethylhexadecanoate (IV) was prepared by reaction of the cadmium reagent from 1-bromo-4-ethylhexane with ω-carbethoxynonoyl chloride.



IV



V

Clemmensen reduction of the keto ester in alcohol, followed by saponification, yielded the desired acid. 15-Ethylheptadecanoic acid (III) was prepared by a similar sequence of reactions, proceeding by way of ethyl 9-keto-15-ethylheptadecanoate (V). The 2-ethyl-1-butanol was purified by careful fractionation through a 3-foot column, and it was converted to the bromide or chloride by methods which avoid rearrangement; so the final acids were purified without difficulty.

EXPERIMENTAL

All melting points are corrected. All distillations, unless otherwise specified, were through a half-meter Podbielniak type column with heated jacket and partial reflux head.

1-Bromo-2-ethylbutane (5). Two liters of commercial 2-ethyl-1-butanol was distilled through a 3-foot column packed with glass helices, and equipped with heated jacket and total reflux head. After three passes, collecting successively narrower cuts, there was obtained 355 g. of alcohol of b.p. 148.3–148.5° (753 mm.). Higher-boiling fractions contained n-hexyl alcohol. The bromide was prepared from 255 g. (2.5 moles) of the pure 2-ethyl-1-butanol and 248 g. (0.91 mole) of phosphorus tribromide, essentially according to the method of Noller and Dinsmore (6). Distillation through the 3-foot packed column yielded 196.6 g. (47.6%) of bromide boiling at 73.8–74.7° (70 mm.).

1-Chloro-2-ethylbutane. Employing the method of Whitmore and Karnatz (7), in order to avoid rearrangement, a solution of 55.3 g. (0.54 mole) of pure 2-ethyl-1-butanol in 44

ml. of dry pyridine was treated during two hours with 90 g. (0.76 mole) of purified thionyl chloride. After heating at 70–80° for three hours, the mixture was diluted with water and hydrochloric acid. The chloride layer was washed with 3 *N* hydrochloric acid, water, and saturated sodium chloride solution, then dried and distilled; yield, 37.5 g. (55%), b.p. 126.5–127.6° (753 mm.).

4-Ethyl-1-hexanol. A Grignard reagent was prepared from 82.5 g. (0.5 mole) of 1-bromo-2-ethylbutane in 400 ml. of ether, in an atmosphere of nitrogen. Ethylene oxide (0.75 mole) was then passed into the solution during about two hours, at −6 to −10°. The mixture was then heated, first in ether, then in benzene, according to the usual published procedures (8). After decomposition of the organometallic complex and separation of the benzene solution, the aqueous phase was extracted twice with benzene. After the extracts had been washed with water, sodium carbonate solution, water, and saturated sodium chloride solution, solvent was removed and the residue distilled. After a fore-run of 18.1 g. (b.p. 53–93° at 20 mm.) the product was collected at 93–97° (20 mm.), 90% boiling at 96°; yield, 23.4 g. (37.5%). A center cut was used for analysis.

Anal. Calc'd for $C_8H_{18}O$: C, 73.79; H, 13.93.
Found: C, 73.78; H, 14.16.

4-Ethyl-1-hexanol was also prepared from 2-ethylbutylmagnesium chloride and ethylene oxide, but the yield (39%) was essentially the same as that obtained with the bromide. This is consistent with the report of Huston and Langham (9) that the reaction of isobutylmagnesium chloride with ethylene oxide gives a much lower yield than obtained with the straight-chain chlorides.

1-Bromo-4-ethylhexane was prepared from 23.0 g. (0.177 mole) of the alcohol with gaseous hydrogen bromide by the usual procedure (10). Distillation of the product yielded 28.2 g. (83%), b.p. 83–84° (17 mm.). A center cut was used for analysis. The analytical figures indicate a small impurity, probably 3,6-diethyloctane from coupling of the Grignard reagent used in preparing 4-ethyl-1-hexanol. The high carbon content of the alcohol prevents detection of this impurity by analysis of that compound. This hydrocarbon is easily removed at the next stage of the synthesis.

Anal. Calc'd for $C_8H_{17}Br$: C, 49.73; H, 8.87; Br, 41.41.
Found: C, 50.66; 50.75; H, 9.04, 9.25; Br, 40.44.

6-Ethyl-1-octanol was prepared as described for 4-ethyl-1-hexanol. From 27.9 g. of 1-bromo-4-ethylhexane, the yield of alcohol of b.p. 121–123.5° (18 mm.) was 9.85 g. (43%). For analysis there was used a center cut of b.p. 122.5° (18 mm).

Anal. Calc'd for $C_{10}H_{22}O$: C, 75.87; H, 14.01.
Found: C, 75.40; H, 14.10.

1-Bromo-6-ethyloctane, prepared by the method used for 1-bromo-4-ethylhexane, was obtained in 71% yield, b.p. 121–123° (19 mm.). For analysis there was used a center cut of b.p. 121–121.8° (19 mm.).

Anal. Calc'd for $C_{10}H_{21}Br$: Br, 36.13 Found: Br, 36.37.

Ethyl 10-keto-14-ethylhexadecanoate (IV). A solution of cadmium reagent in 60 ml.of benzene was prepared in the manner previously described (11) from 14 g. (0.0725 mole) of 1-bromo-4-ethylhexane. After treatment of the boiling solution with 14.4 g. (0.058 mole) of ω-carbethoxynonoyl chloride in 30 ml. of benzene, the mixture was refluxed for two hours, then worked up in the usual fashion (11) for keto esters. Distillation gave 1.20 g. of fore-run, b.p. 90–192° (5–1 mm.), and 10.6 g. (45% yield, based on bromide) of keto ester, IV, b.p. 192–196° (1 mm.).

Anal. Calc'd for $C_{20}H_{38}O_3$: C, 73.57; H, 11.73.
Found: C, 72.64; H, 11.80.

The corresponding *keto acid*, obtained by saponification of the ester with alcoholic potassium hydroxide, was obtained as fine plates, m.p. 45.8–47.4°, after three crystallizations from ligroin (b.p. 36–38°).

Anal. Calc'd for $C_{18}H_{34}O_3$: C, 72.43; H, 11.48.
Found: C, 72.33; H, 11.49.

Ethyl 9-keto-15-ethylheptadecanoate (*V*) was prepared as described for keto ester, IV. From 9.54 g. (0.043 mole) of 1-bromo-6-ethyloctane and 8.10 g. (0.0345 mole) of ω-carbethoxycaprylyl chloride (12), the yield of keto ester, V, was 7.13 g. (48.5%, based on bromide), b.p. 175–181° (*ca.* 0.5 mm.).

Anal. Calc'd for $C_{21}H_{40}O_3$: C, 74.07; H, 11.84.

Found: C, 72.65, 72.88; H, 11.67, 11.81.

The *keto acid* was obtained from ester, V, by saponification with alcoholic potassium hydroxide. After three crystallizations from ligroin (b.p. 34–40°), it separated as blades of m.p. 43.6–44.2°.

Anal. Calc'd for $C_{19}H_{36}O_3$: C, 73.03; H, 11.62.

Found: C, 73.21; H, 11.31.

Reduction of the keto esters was accomplished by Schneider and Spielman's modifilation (13) of the Clemmensen method. For 0.027 mole of keto ester in 200 ml. of absolute alcohol there was used 100 g. of amalgamated mossy zinc, and refluxing was continued for 36 hours, the solution being saturated at 0° with dry hydrogen chloride at the beginning of the reaction and after 14 hours under reflux. The products were isolated by dilution of the reaction mixture with water and extraction with benzene. The yield of *ethyl 14-ethylhexadecanoate* was 85.5%, b.p. 168–173° (*ca.* 0.5 mm.). An analytical sample was taken at 170–171°.

Anal. Calc'd for $C_{20}H_{40}O_2$: C, 76.86; H, 12.90.

Found: C, 76.14; H, 12.60.

The yield of *ethyl 15-ethylheptadecanoate* was 62%, b.p. 157–165° (*ca.* 0.5 mm.).

Anal. Calc'd for $C_{21}H_{42}O_2$: C, 77.24; H, 12.97.

Found: C, 77.34; H, 12.89.

In this distillation, there was a relatively large forerun (more than half the weight of the ester fraction), which may have arisen in part from impurities in keto ester, V, for the analysis of this keto ester (*cf.* above) was in rather poor agreement with theory.

14-Ethylhexadecanoic acid (*II*). Saponification of 6.98 g. of ethyl 14-ethylhexadecanoate by heating under reflux for one hour with 50 ml. of 8% alcoholic potassium hydroxide gave a quantitative yield of crude acid, m.p. 38.8–41.4° (cloudy). After one crystallization from acetone, there was obtained 4.92 g. of fine lustrous needles, m.p. 41.8–42.9°. After two additional crystallizations from methanol, the m.p. was essentially the same, 42.0–42.9°.

Anal. Calc'd for $C_{18}H_{36}O_2$: C, 75.99; H, 12.76; mol. wt., 284.5.

Found: C, 76.15; H, 12.43; mol. wt., 284.1.

The *amide* was prepared by dropping a dioxane (4 ml.) solution of acid chloride from 0.5 g. of acid into 12 ml. of cold concentrated ammonium hydroxide; crude yield, 0.49 g., m.p. 73–79°. After three crystallizations from ligroin, there was obtained 0.35 g. of fine blades, m.p. 78.8–79.9°.

Anal. Calc'd for $C_{18}H_{37}NO$: C, 76.26; H, 13.16.

Found: C, 76.04; H, 13.26.

The *tribromoanilide*, prepared as previously described (8b), was obtained in 81% yield, m.p. 86–95°, after one crystallization from ligroin (b.p. 80–96°). After successive crystallizations from ethanol, ligroin, and acetone, soft short needles were obtained melting at 100.2–101.0°.

Anal. Calc'd for $C_{24}H_{38}Br_3NO$: C, 48.33; H, 6.42.

Found: C, 48.31; H, 6.93.

15-Ethylheptadecanoic acid (*III*) was prepared as described for II by saponification of 3.67 g. of the corresponding ester; yield 3.17 g. (95%), m.p. 31–35°. After three crystallizations from methanol there was obtained 1.35 g. of acid as clusters of fine needles, m.p. 36.7–37.4°.

Anal. Calc'd for $C_{19}H_{38}O_2$: C, 76.45; H, 12.83; mol. wt., 298.5.

Found: C, 76.94; H, 12.60; mol. wt., 299.3, 298.9.

Derivatives of this acid were prepared as described for the homolog. The crude amide, obtained in 98% yield, melted at 72–75°. After three crystallizations from ligroin,

one from methanol, and one from acetone (m.p. not changing during latter crystallizations), this *amide* melted at 79.0–81.1°, after softening at 76°. It appears to be polymorphic, for it melts completely at once when placed in a bath preheated to 80°.

Anal. Calc'd for $C_{19}H_{39}NO$: C, 76.71; H, 13.21.
Found: C, 76.25; H, 13.16.

The *tribromoanilide* was obtained in 94% yield of m.p. 89–95°, and after three crystallizations from ethanol it was obtained as rosettes of needles melting at 101.5–102.2°.

Anal. Calc'd for $C_{25}H_{40}Br_3NO$: C, 49.21; H, 6.60.
Found: C, 49.44; H, 6.78.

SUMMARY

14-Ethylhexadecanoic acid and 15-ethylheptadecanoic acid have been prepared. Although these acids have symmetrical end-groups, they do not have relatively high melting points, as do the iso acids, but melt more than twenty-five degrees below the normal isomers of the same molecular weights.

Berkeley, Calif.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

BRANCHED-CHAIN FATTY ACIDS. IX. SYNTHESIS OF ACIDS WITH SYMMETRICAL END-GROUPS

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In the preceding paper (1) of this series, there was reported the synthesis of a C_{18} acid (I) and a C_{19} acid (II) with symmetrical end-groups in which the branching groups were ethyl. These acids proved to have melting points more than twenty-five degrees below those of the normal isomers.

$$
\begin{array}{l}
CH_3\text{—}(CH_2)_n \diagdown \\
\qquad\qquad\qquad\quad CH\text{—}(CH_2)_m\text{—}CO_2H \\
CH_3\text{—}(CH_2)_n \diagup
\end{array}
$$

I	n = 1, m = 12	IV	n = 2, m = 16
II	n = 1, m = 13	V	n = 5, m = 10
III	n = 1, m = 18	VI	n = m = 7

In the present paper there is reported the synthesis of four higher molecular weight acids with symmetrical end-groups: 20-ethyldocosanoic acid (III), 18-*n*-propylheneicosanoic acid (IV), 12-*n*-hexyloctadecanoic acid (V), and 9-*n*-octylheptadecanoic acid (VI). The melting points of these acids, respectively, are 64.8–65.5°, 51.9–52.2°, 28.3–28.7°, and 9–14°. It is seen that as the branching group becomes larger the melting point drops progressively further below that of the normal isomer, and is lowest for the C_{25} acid, VI, in which the tertiary carbon carries three chains of equal length. Thus, any apparent symmetry about the tertiary carbon does not tend to raise the melting point, but the melting point becomes progressively lower as the branching end-group becomes larger. As the tertiary carbon is shifted further toward the carboxyl, thus shortening the chain carrying carboxyl, the melting point must begin to increase again at some point, for didodecylacetic acid (2) melts about 17° below the normal isomer. It is of interest that in the series of branched-chain alkanes synthesized by Whitmore, Sutherland, and Corby (3), the melting point again becomes progressively further below that of the normal isomer as the tertiary carbon carrying two of the same group approaches the center of the chain.

Of the types of acids which it was previously suggested (4) might have melting points within the "excluded region" of about ten degrees below the melting point of the normal isomer, there have now been eliminated all but the acids having on a quaternary carbon either four groups of equal size or three equal groups and

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the carboxyl.[2] Further attempts to prepare acids of this type are in progress; however, such acyclic acids of high molecular weight have not yet been found in nature. It seems likely that acids from natural sources with melting points in the "excluded region" are mixtures. There has already been presented (5) convincing evidence that two acids from tubercle bacillus, which melt in this region, are mixtures of normal isomers rather than homogeneous substances.

The two symmetrical acids reported in the previous paper (1) were prepared by chain extension of the commercially available 2-ethyl-1-butanol, but alcohols with larger symmetrical end-groups are not available. Those required for synthesis of acids, III and IV, were prepared by high-pressure hydrogenation of unsaturated esters obtained by the illustrated sequence of reactions.

$$\mathrm{RMgX} + \mathrm{RC(=O){-}(CH_2)_n{-}CO_2C_2H_5} \rightarrow \xrightarrow{H_2O} \mathrm{RC(OH)(R){-}(CH_2)_n{-}CO_2C_2H_5}$$

VII $R = C_2H_5, n = 8$
VIII $R = n\text{-}C_3H_7, n = 7$
IX $R = n\text{-}C_6H_{13}, n = 10$
X $R = n\text{-}C_8H_{17}, n = 7$

$$\mathrm{RC(OH)(R){-}(CH_2)_n{-}CO_2C_2H_5} \xrightarrow{I_2,\ 180\text{–}190^\circ} \text{mixture of unsaturated esters}$$

$$\mathrm{RCH(R){-}(CH_2)_n{-}CH_2OH} \xleftarrow{H_2,\ CuCr} \text{mixture of unsaturated esters}$$

XI $R = C_2H_5, n = 8$
XII $R = n\text{-}C_3H_7, n = 7$

$$\text{mixture of unsaturated esters} \xrightarrow{H_2,\ Pt} \mathrm{RCH(R){-}(CH_2)_n{-}CO_2C_2H_5}$$

XIII $R = n\text{-}C_6H_{13}, n = 10$
XIV $R = n\text{-}C_8H_{17}, n = 7$

The carbon chains of alcohols, XI and XII, were extended as before (1) by reaction of the corresponding cadmium reagents with the appropriate ester acid chlorides. The resultant keto esters, XV and XVI, were converted to the desired branched-chain acids (III, IV)

$$\mathrm{(C_2H_5)_2CH{-}(CH_2)_9{-}C(=O){-}(CH_2)_8{-}CO_2C_2H_5}$$

XV

$$\mathrm{(C_3H_7)_2CH{-}(CH_2)_8{-}C(=O){-}(CH_2)_7{-}CO_2C_2H_5}$$

XVI

by Clemmensen or Wolff-Kishner reduction of the keto group.

[2] There has just appeared [Sperber, Papa, and Schwenk, *J. Am. Chem. Soc.*, **70**, 3091 (1948)] a report of synthesis of trialkylacetic acids with three of the same alkyl group. Although tri-*n*-propylacetic acid melted at 65.5–67.5°, tri-*n*-butylacetic acid melted at 35.5–37.5°, and tri-*n*-amylacetic acid presumably was an oil since no m.p. was reported. Thus, it appears that high molecular weight acids of this type do not have relatively high melting points. (Footnote added Oct. 12, 1948).

For synthesis of acids, V and VI, no further chain extension was necessary. The unsaturated esters obtained from keto esters, IX and X, were hydrogenated at low pressure with platinum catalyst, and saponification of the resultant saturated esters (XIII, XIV) gave the desired acids (V, VI).

Ethyl 12-ketooctadecanoate (IX) was prepared by esterification of the keto acid obtained by oxidation of crude 12-hydroxyoctadecanoic acid from saponification of hydrogenated castor oil. The keto acid was separated with difficulty from stearic acid present in the hydrogenated castor oil, but the ethyl ester (IX) was easily purified by fractional distillation. The other three starting keto esters (VII, VIII, X) were prepared in good yield by reaction between the appropriate dialkylcadmium reagent and ester acid chloride. Since the next step in the synthesis is reaction of the keto ester with the same Grignard reagent used for making the cadmium reagent, it was thought possible that an easier approach to the hydroxy ester would be reaction of the Grignard reagent directly with the ester acid chloride, according to the following scheme.

$$2RMgBr + ClC(=O)-(CH_2)_n-CO_2C_2H_5 \rightarrow \xrightarrow{H_2O} RC(OH)(R)-(CH_2)_n-CO_2C_2H_5$$

Unfortunately, considerably lower over-all yields were obtained by this procedure, for the reactivity of the acid chloride group toward the Grignard reagent is only slightly greater than the reactivity of the ester group. In the preparation of 10-ethyl-1-dodecanol (XI), the over-all yield based on ω-carbethoxynonoyl chloride (the more valuable starting material) was 49% in the process proceeding by way of preparation and isolation of the keto ester, but only 18% when the ester acid chloride was treated directly with the Grignard reagent.

The selective reaction of a Grignard reagent with a keto ester to give a hydroxy ester has previously been used (6) as an approach to branched-chain acids. The over-all yields of saturated branched-chain acids or esters have been in the range, 20–44%. A major difficulty has been the unstirrable mass obtained in the Grignard reaction. Since the yields in preparation of γ-valerolactones (7) by a nearly identical process were doubled by addition of benzene to break up this unstirrable mass, this device was tried in the present work. Results were favorable, in that the over-all yields of saturated esters (XIII, XIV) or saturated alcohols (XI, XII) were in the range, 39–55%.

It would seem that an additional improvement in this process might be realized by introducing steric hindrance around the ester grouping. This possibility was investigated by the preparation of cyclohexyl 12-ethyloctadecenoate starting with ethylmagnesium iodide and cyclohexyl 12-ketooctadecanoate. The over-all yield of this unsaturated ester was 73%. By hydrogenation and transesterification, an over-all yield (based on keto ester) of ethyl 12-ethyloctadecanoate (XVII) amounting to 54% was obtained.

$$C_6H_{13}CH(C_2H_5)-(CH_2)_{10}-CO_2C_2H_5$$

XVII

Thus, the use of the cyclohexyl ester appears an advantage, although the increase in boiling point is a handicap with higher molecular weight compounds, and trans-esterification is necessary if hydrogenation is carried out in ethanol.

A major problem encountered in synthesis of pure compounds by the scheme used in the present work is separation of the large number of compounds obtained from the reaction between a Grignard reagent and a keto ester. When the saturated alcohol (XI or XII) is the desired end-product, there must be considered the separation of (*a*) the diol, A, from hydrogenation of the starting keto ester; (*b*) the alcohol, B, from hydrogenation of the unsaturated ketone resulting from dehydration of the keto alcohol arising from reaction of the Grignard reagent with both keto and ester group; (*c*) the hydrocarbon, C, arising from reaction of three moles of Grignard reagent with the keto ester, dehydration and hydrogenation. The diol, D, arising from reaction of only one mole of Grignard reagent with the ester group and no reaction with the keto groups would be expected in very small amount.

$$\mathrm{R\overset{\displaystyle OH}{\overset{|}{C}}H{-}(CH_2)_n{-}CH_2OH}$$

A

$$\mathrm{R_2CH{-}(CH_2)_n{-}\overset{\displaystyle OH}{\overset{|}{C}}HR}$$

B

$$\mathrm{R_2CH{-}(CH_2)_n{-}CHR_2}$$

C

$$\mathrm{R\overset{\displaystyle OH}{\overset{|}{C}}H{-}(CH_2)_n{-}\overset{\displaystyle OH}{\overset{|}{C}}HR}$$

D

From a consideration of the contribution to boiling point of the various groups present in these by-products, it was estimated that when R is ethyl compounds A and B would boil about 20° above the desired alcohol, XI, while compound C would have about the same boiling point and compound D would boil about 40° above XI. Since the hydrocarbon, C, is inert, its presence in small amount in the desired alcohol is no disadvantage, for it is easily separated from the higher molecular weight compounds obtained later in the synthesis. The other compounds should be easily separated in an efficient half-meter fractionating column. This proved the case, and a sample of crystalline diol, A, was isolated from the fraction boiling about 20° above the desired alcohol, XI. When R is propyl, all products except A should boil 20° or more above XII; however, the diol, A should boil no more than 10–15° above XII. This proved to be the case, and the construction of a four-foot Podbielniak type column was necessary for efficient separation of this diol.

When the saturated ester (XIII or XIV) is the desired product, separation of the products obtained by low-pressure hydrogenation must be considered. When R is octyl, the separation is simple, for all by-products differ in boiling point by 40° or more from the desired ester. When R is hexyl, the only separation problem concerns the unreacted keto ester, IX. This is reduced, in part, by platinum at low pressure to give the corresponding hydroxy ester, which was separated from the saturated ester, XIII, with difficulty, even in the four-

foot column. This difficulty was avoided, however, by fractional distillation of the unsaturated ester, before hydrogenation, for the keto ester, IX, boils at least ten degrees below the corresponding hydroxy ester. Some loss of unsaturated ester may have occurred during the long heating necessary for fractional distillation, for the yield of XIII (39%) was appreciably lower than obtained for XIV (55%).

EXPERIMENTAL

Microanalyses are by C. W. Koch and V. H. Tashinian. All melting points are corrected; all boiling points are uncorrected. All distillations, unless otherwise specified, were carried out in a half-meter Podbielniak type column with heated jacket and partial reflux head.

TABLE I

KETO ESTERS

ESTER	YIELD, %	B.P., °C	MM. HG	n^{20}_D	ANAL. CALC'D C	ANAL. CALC'D H	ANAL. FOUND C	ANAL. FOUND H
VII	88–89	169–173	10	1.4429	69.38	10.82	68.68	10.86
VIII	94.5	165–167	7	1.4420	69.38	10.82	68.96	10.52
X	45[a]	211–212	5	[b]	73.07	11.61	73.12	11.28
XV	74	235–240	1	solid			[c]	
XVI	72	236–240	1	1.4550	76.04	12.27	76.03	12.31

[a] The ω-carbethoxycaprylyl chloride used in this preparation was prepared from an old sample of half ester which had disproportionated (9) to considerable di-acid chloride and di-ester. The di-ester is inert, but the di-acid chloride yielded *9,17-hexacosanedione*, b.p. 247–248° (2 mm.); 19.7 g. isolated from an 0.33 mole run. After two crystallizations from acetone, this diketone melted at 92.8–93.4°.

Anal. Calc'd for $C_{26}H_{48}O_2$: C, 78.88; H, 12.71. Found: C, 79.09; H, 12.88.

[b] After two crystallizations from acetone, m.p. 38.2–38.7°.

[c] Not analyzed, characterized as acid, *cf.* Table II.

Alkyl halides. The simple normal halides used as starting materials were purified commercial products or obtained from commercial alcohols by usual methods. All were distilled through the half-meter column or a 1-meter column packed with glass helices, and collected over a range of about one degree. Branched-chain bromides were prepared from anhydrous hydrogen bromide taken from a cylinder, following the usual procedure (8). *10-Ethyl-1-bromododecane* was obtained in 83% yield, b.p. 159.5–161.5° (11 mm.), n^{20}_D 1.4653.

Anal. Calc'd for $C_{14}H_{29}Br$: C, 60.66; H, 10.55.

Found: C, 59.47; H, 10.80.

9-n-Propyl-1-bromododecane was obtained in 63% yield, b.p. 168–171.5° (13 mm.), n^{20}_D 1.4648.

Anal. Calc'd for $C_{15}H_{31}Br$: C, 61.84; H, 10.73.

Found: C, 61.68; H, 10.93.

Keto esters were prepared by the usual method (9) from dialkylcadmium reagent and ester acid chloride and isolated as described previously for keto esters. Data for the products are found in Tables I and II, yields being based on ester acid chloride. For esters, VII, VIII, and X, there were used two equivalents of alkyl halide (ethyl iodide, *n*-propyl bromide, and *n*-octyl bromide) for one of ester acid chloride. For esters, XV and XVI, the equivalency of branched-chain halide was 1.25.

Ethyl 12-ketooctadecanoate (IX). A suspension of 200 g. (0.67 mole) of crude 12-hydroxyoctadecanoic acid (from saponification of commercial hydrogenated castor oil) in 1100 ml. of glacial acetic acid was stirred vigorously as there was added during two hours a solution of 50 g. (0.50 mole) of chromic anhydride in 270 ml. of glacial acetic acid. The temperature of the mixture did not rise above 37°. After stirring, without heating, had been continued for an additional two hours, the mixture was poured, with stirring, into ten liters of water. The solid product was crystallized from acetone, after treatment with Norit. The yield of pale lavender keto acid, m.p. 80.5–83°, was 155 g. (78%, assuming homogeneous starting material). The impure acid so obtained was esterified by heating for two hours with 450 ml. of absolute ethanol containing 24.5 g. of hydrogen chloride gas. After dilution of the reaction mixture with water and extraction with ether, the ester was distilled. After a fore-run of 15 g., consisting largely of ethyl stearate, the crystalline keto ester was collected at 199–200° (3.0 mm.), m.p. 35–37.5°, wt. 132.2 g. (61% yield from crude hydroxy acid).

Saponification of a sample of the ester and crystallization of the keto acid from acetone yielded lustrous blades, m.p. 82.0–82.3°. Perrotte (11) reported m.p. 81.0–81.5°.

10-Ethyl-1-dodecanol (XI). (A) A Grignard reagent was prepared in an atmosphere of nitrogen from 63 g. of ethyl iodide and 8.9 g of magnesium in 200 ml. of ether. After about half the ether had been distilled, 500 ml. of dry thiophene-free benzene was added

TABLE II

DERIVATIVES OF KETO ESTERS

ESTER	DERIVATIVE	SOLVENT FOR CRYST.	M.P., °C.
VII	Semicarbazone	Acetone	74.6–75.8[a]
VIII	Keto acid[b]	Hexane	55.9–56.4
XV	Keto acid[c]	Acetone	67.0–67.8

[a] Polymorphic, remelts at 79.5–81.0°. Paraskova (10) reports m.p. 81.0–82.0°.
[b] Mol. wt. found, 217.0 (calc'd 214.3).
[c] Calc'd for $C_{24}H_{46}O_3$: C, 75.30; H, 12.10. Found: C, 75.53; H, 12.40.

and the solution forced under nitrogen pressure into a separatory funnel This solution was added dropwise, during one hour, to a stirred solution of 87.4 g. of ethyl 10-ketododecanoate (VII) in 450 ml. of benzene, the mixture being cooled in an ice-salt bath just insufficiently to freeze the benzene. After addition was complete, stirring was continued for an additional twenty minutes, then the organometallic complex was decomposed with ice and acid. The organic layer and an additional benzene extract of the aqueous phase were washed with water, 5% sodium carbonate solution, water, and saturated sodium chloride solution. After solvent had been distilled, last traces in a vacuum, the residue was heated for one hour with a few crystals of iodine, at 180–190°. Distillation of the unsaturated esters from a Claisen flask yielded 75.3 g. of b.p. 164–170° (10 mm.). This distillate was hydrogenated with 15 g. of copper chromite catalyst (12) at 250° and an initial cold pressure of 3180 lbs. per sq. in. The final pressure at 250° was 2870 lbs., and hydrogenation was complete in 3 hrs., 10 mins. from the time shaker and heater were started. Distillation of the product at 10 mm. pressure gave the following fractions: (*a*) 10-ethyl-1-dodecanol, wt. 43.1 g., b.p. 155–160°; (*b*) intermediate fraction, wt. 2.1 g.; (*c*) 1,10-dodecanediol, wt. 12.9 g., b.p. 174.5–175.5°. The yield of alcohol, XI, is 55%, based on keto ester. For the sample analyzed, n_D^{22} 1.4487.

Anal. Calc'd for $C_{14}H_{30}O$: C, 78.43; H, 14.11.
Found. C, 77.82; H, 13.91.

(B) A solution of ethylmagnesium iodide, prepared as in Method (A) from 38 g. of ethyl iodide, was added during 80 minutes to a stirred solution of 29.8 g. of ω-carbethoxynonoyl chloride in 85 ml. of benzene, with cooling in ice and salt. The reaction mixture was worked

up, and the unsaturated ester obtained and hydrogenated as above. Distillation of the product at 10 mm. pressure gave the following fractions: (*a*) 10-ethyl-1-dodecanol, wt. 4.6 g., b.p. 153–158°; (*b*) intermediate; (*c*) 1,10-dodecanediol, wt. 3.5 g., b.p. 172.5–173°. Thus, the over-all yield of XI is only 18%.

The *phenylurethan of XI*, after two crystallizations from hexane, melted at 54–56.1°. It is apparently polymorphic since a sample melted completely at once when placed in a bath at 55.5°.

Anal. Calc'd for $C_{21}H_{35}NO_2$: C, 75.63; H, 10.58
Found: C, 75.29; H, 10.26.

1,10-Dodecanediol, Frac. (*c*), Method (A), after repeated crystallization from hexane-acetone, melted at 38.6–39.8°.

Anal. Calc'd for $C_{12}H_{26}O_2$: C, 71.23; H, 12.95.
Found: C, 71.16; H, 12.69.

Ethyl 10-ethyldodecanoate was prepared by hydrogenation of 14.9 g. of unsaturated esters [obtained as in Method (A) above] at room temperature and low pressure, with 0.3 g. of platinum oxide catalyst in 100 ml. of 95% ethanol. Hydrogenation was complete in 40 minutes, and distillation gave 11.4 g. (64% over-all yield from keto ester) of saturated ester, b.p. 162–163° (10 mm.).

9-n-Propyl-1-dodecanol (XII) was prepared according to Method (A) described for alcohol, XI. From 0.5 mole of ethyl 9-ketododecanoate and *ca.* 0.58 mole of *n*-propylmagnesium bromide, distillation through a 4-foot Podbielniak type column at 4 mm. pressure of the products obtained after high-pressure hydrogenation gave the following fractions: (*a*) 9-*n*-propyl-1-dodecanol, wt. 54.3 g. (45.5%, over-all) b.p. 150–153°, n_D^{20} 1.4507; (*b*) intermediate, wt. 3.6 g.; (*c*) 1,9-dodecanediol, wt. 18.9 g., b.p. 167–172°.

The alcohol, XII, was characterized as the *α-naphthylurethan*, which crystallized in nodular clusters from acetone and appears to be polymorphic. After four crystallizations, the m.p. was 51–57°, but complete melting occurred at once when the sample was placed in a bath at 55°.

Anal. Calc'd for $C_{26}H_{38}NO_2$: N, 3.54. Found: N, 3.47.

The 3,5-dinitrobenzoate of this alcohol is an oil and the *p*-phenylbenzoate is a low-melting solid.

1,9-dodecanediol, Frac. (*c*) above, after repeated crystallization from hexane-acetone melted at 38.2–38.8°.

Anal Calc'd for $C_{12}H_{26}O_2$: C, 71.23; H, 12.95.
Found: C, 71.30; H, 13.13.

Ethyl 12-n-hexyloctadecanoate (XIII). Starting with 0.12 mole of ethyl 12-ketooctadecanoate (IX) and the Grignard reagent from 0.21 mole of *n*-hexyl bromide, a mixture of unsaturated esters was prepared as described under Method (A) for 10-ethyl-1-dodecanol. The lower ratio of keto ester was used in order to simplify the separation of this starting material. Distillation through the column of the mixture remaining after dehydration yielded 4.3 g. of fore-run and 33.1 g. (69% yield) of pale yellow unsaturated esters, b.p. 211–215° (2 mm.). There was 11 g. of distillation residue. The ester fraction was immediately hydrogenated at room temperature and low pressure with 0.2 g. of platinum oxide catalyst in 125 ml. of 95% ethanol. The ester was sparingly soluble in ethanol and hydrogenation required 12 hours. After solution of the product in ether, removal of catalyst, and distillation of solvent, the ester was distilled; yield 18.5 g. (39%), b.p. 213–215° (2 mm.), n_D^{20} 1.4508.

Anal. Calc'd for $C_{26}H_{52}O_2$: C, 78.72; H, 13.21.
Found: C, 78.58; H, 13.38.

Ethyl 9-n-octylheptadecanoate (XIV) was prepared in the same manner as described for XIII except that the unsaturated esters were distilled from a Claisen flask. In a run starting with 0.067 mole of ethyl 9-ketoheptadecanoate and the Grignard reagent from 0.11 mole of *n*-octyl bromide, the yield of crude unsaturated esters was 21.5 g. After hydrogenation as for XIII, distillation yielded the following fractions: (*a*) fore-run, wt. 4.3 g.

and containing 1.0 g. of ethyl 9-ketoheptadecanoate; (*b*) ethyl 9-*n*-octylheptadecanoate, wt. 15.3 g. (55% over-all yield), b.p. 224–227° (2 mm.), n_D^{25} 1.4512.

Anal. Calc'd for $C_{27}H_{54}O_2$: C, 78.95; H, 13.26.

Found: C, 78.98; H, 13.15.

Ethyl 12-ethyloctadecanoate (*XVII*). Since the ethyl ester, IX, had been prepared in quantity, cyclohexyl 12-ketooctadecanoate was prepared by allowing a mixture of 61.5 g. (0.612 mole) of cyclohexanol, 50 g. (0.153 mole) of ethyl 12-ketooctadecanoate (IX), and 6.2 g. of hydrogen chloride gas to stand at room temperature for eight days. Solvent was then removed in a vacuum, last traces at 2.5 mm. and 180°, and the residue (54.8 g.) was used for the Grignard reaction.

The Grignard reagent from 14.9 g. (0.095 mole) of ethyl iodide, in 50 ml. of ether and 110 ml. of benzene, was added dropwise to a stirred solution of 30 g. (0.079 mole) of cyclohexyl 12-ketooctadecanoate in 110 ml. of benzene, the temperature being maintained by external cooling at 5–10°. Addition was completed in 15 minutes, and five minutes later the mixture had become an unstirrable jelly, so stirring was continued for an additional 30 minutes at 25–30°. The mixture was worked up and the hydroxy ester dehydrated as described under Method (A) for preparation of 10-ethyl-1-dodecanol (XI). The unsaturated esters, distilled from a Claisen flask, weighed 22.1 g. (73%), b.p. 213–220° (4 mm.).

The unsaturated ester was immediately hydrogenated at low pressure and room temperature with 0.15 g. of platinum oxide catalyst in 150 ml. of 95% ethanol. Hydrogenation was complete in one hour. After catalyst had been removed by filtration, 100 ml. of absolute ethanol and 10.6 ml. of concentrated sulfuric acid were added, and the mixture was heated under reflux for 90 minutes. The ethyl ester, XVII, was isolated by dilution of the reaction mixture with water, extraction with benzene, and distillation; yield 14.5 g. (54% over-all), b.p. 191–194° (3 mm.), n_D^{30} 1.4479. There was 2.5 g. of distillation residue, and the yield on the hydrogenation and trans-esterification step is probably subject to improvement.

Anal. Calc'd for $C_{22}H_{44}O_2$: C, 77.58; H, 13.02.

Found: C, 77.33; H, 12.96.

20-Ethyldocosanoic acid (*III*). The keto ester, XV, (23.8 g.) was reduced by the Schneider and Spielman modification (6) of the Clemmensen method. The yield of semi-solid *ethyl 20-ethyldocosanoate* was 15.2 g. (66%), b.p. 220–223° (*ca.* 1 mm.).

Anal. Calc'd for $C_{26}H_{52}O_2$: C, 78.72; H, 13.21.

Found: C, 79.28; H, 13.86.

By saponification of 19.1 g. of the ester and crystallization from acetone of the resultant acid, there was obtained 17.3 g. (93%) of 20-ethyldocosanoic acid, m.p. 60.5–62°. After four additional crystallizations from hexane, the constant m.p. of 64.8–65.5° was reached.

Anal. Calc'd for $C_{24}H_{48}O_2$: C, 78.17; H, 13.14; mol. wt., 368.7.

Found: C, 78.53; H, 13.40; mol. wt., 369.0.

For preparation of the amide, 0.7 g. of acid was allowed to stand overnight with 0.45 g. of thionyl chloride then heated under reflux until no further gas evolution was apparent (*ca.* 45 mins.). Excess thionyl chloride was removed by heating *in vacuo*, and to the residual acid chloride there was added in one portion, with immediate shaking, 10 ml. of ice-cold concentrated ammonium hydroxide. After filtration of the curdy precipitate and one crystallization from acetone, 0.65 g. of *20-ethyldocosanamide* was obtained. After four additional crystallizations from acetone and two from hexane, the pure amide was obtained as fine white blades, m.p. 90.2–90.6°.

Anal. Calc'd for $C_{24}H_{49}NO$: C, 78.40; H, 13.43.

Found: C, 78.54; H, 13.55.

For preparation of the *tribromoanilide*, the acid chloride, prepared as described above from 0.7 g. of acid, was heated for 2 hours on a steam-bath with 0.5 g. of 2,4,6-trobromoaniline. After one crystallization from ethanol, 0.8 g. of fine needles was obtained. After one additional crystallization from ethanol and three from benzene-hexane, the pure tribromoanilide was obtained, m.p. 104.7–105.3°.

Anal. Calc'd for $C_{30}H_{50}Br_3NO$: C, 52.95; H, 7.41.
Found: C, 53.17; H, 7.53.

18-n-Propylheneicosanoic acid (IV). The keto ester, XVI, (27.9 g.) was reduced by the modified Wolff-Kishner method, following essentially the procedure of Huang-Minlon (13). After completion of the final heating period and acidification of the cooled and diluted reaction mixture, the precipitated acid was collected; wt. 14.6 g. (58%), m.p. 45–49°. After four crystallizations from acetone, pure 18-*n*-propylheneicosanoic acid was obtained as fine blades, m.p. 51.9–52.2°.

Anal. Calc'd for $C_{24}H_{48}O_2$: C, 78.17; H, 13.14; mol. wt., 368.7.
Found: C, 78.55; H, 13.23; mol. wt., 371.8.

Derivatives of this acid were prepared as described for the isomer, III. The *amide*, after two crystallizations from acetone, had the constant m.p. 82.1–82.4°.

Anal. Calc'd for $C_{24}H_{49}NO$: C, 78.40; H, 13.43.
Found: C, 78.58; H, 13.12.

The *tribromoanilide*, after four crystallizations from benzene-hexane, was obtained as very fine needles which grew in clusters at first and finally converted the solution into a gel, m.p. 92.6–93.6°.

Anal. Calc'd for $C_{30}H_{50}Br_3NO$: C, 52.95; H, 7.41.
Found: C, 53.28; H, 7.43.

12-n-Hexyloctadecanoic acid (V) was obtained by saponification of 17.4 g. of the ester, XIII. The crude acid (16.2 g.) was a liquid which set to a solid on standing overnight. After two crystallizations from acetone, 7.7 g. of the pure acid was obtained as long needles, m.p. 28.3–28.7°.

Anal. Calc'd for $C_{24}H_{48}O_2$: mol. wt., 368.7. Found: mol. wt., 368.0.

The *p-bromoanilide* of this acid was prepared by heating a solution of 1.0 g. of *p*-bromoaniline and the acid chloride from 1.0 g. of acid in 10 ml. of benzene under reflux for 3 hours. The benzene solution was washed with water, dilute hydrochloric acid, water, and sodium bicarbonate solution, then the benzene was distilled. The residue was crystallized twice from hexane (Norit), in which solvent it forms a gel, and twice from methanol. The pure anilide separated from methanol in spherical burrs of needles, m.p. 67.2–67.8°

Anal. Calc'd for $C_{30}H_{52}BrNO$: C, 68.94; H, 10.03.
Found: C, 68.95; H, 9.96.

9-n-Octylheptadecanoic acid (VI) was obtained in 12 g. yield by saponification of 13.7 g. of the ester, XIV. The crude acid was a viscous liquid which crystallized in an ice-salt bath. It was crystallized twice from acetone, cooling to about −30° After the second crystallization, the crystals were washed with acetone cooled to −70°, and the funnel was placed in a desiccator which was immediately evacuated. Evaporation of acetone prevented melting until nearly all solvent was removed, and the oil was left at about 1 mm. pressure for five days. The recrystallized acid, on chilling and being allowed to warm up, melted at 9–14°, n_D^{30} 1.4585.

Anal. Calc'd for $C_{25}H_{50}O_2$: mol. wt., 382.9. Found. mol. wt., 381.5, 381.2

The *p-bromoanilide*, prepared as described for acid, V, after three crystallizations from acetone, was obtained as burrs of fine needles, m.p. 79.7–80.1°.

Anal. Calc'd for $C_{31}H_{54}BrNO$: C, 69.36; H, 10.13.
Found: C, 69.04; H, 9.80.

The amide and tribromoanilide of the acid could not be obtained as satisfactory crystalline derivatives.

SUMMARY

Four new acids with symmetrical end-groups have been prepared. The branching groups were, respectively, ethyl, *n*-propyl, *n*-hexyl, and *n*-octyl. As the end-group became larger, causing the tertiary carbon to approach the middle of the chain, the melting point dropped further below that of the normal

isomer. This behavior is the same type as that observed when a branching methyl group is moved toward the middle of the chain; hence a symmetrical end-group has no tendency to impart to branched-chain acids a relatively high melting point.

In the course of these syntheses, the selective reaction of a Grignard reagent with the keto group in an aliphatic keto ester has been studied, and improved yields have been realized in this reaction.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

BRANCHED-CHAIN FATTY ACIDS. X. SYNTHESIS OF ACIDS WITH BRANCHING METHYL GROUPS NEAR THE CARBOXYL

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In order to make a study of the effect of neighboring branching groups on the rate of hydrolysis of amides, as reported in the next paper of this series, it was necessary to prepare several branched-chain acids with one or more methyl groups on carbons near the carboxyl. The preparation of α-methyl acids is easily accomplished by alkylation of diethyl methylmalonate, followed by hydrolysis and decarboxylation. The two acids prepared for the present work, 2-methyloctadecanoic acid and 2-methyldocosanoic acid, have been synthesized previously (1), and our constants were in good agreement with those previously reported.

Two β-methyl acids, 3-methyloctadecanoic acid (II) and 3-methyltetracosanoic acid (III), were prepared. Both of these acids have also been prepared previously, but by less convenient or less satisfactory procedures. 3-Methyloctadecanoic acid (2) was prepared previously by alkylation of diethyl malonate with 2-bromoheptadecane, no precautions being taken to avoid formation of isomeric secondary bromides during conversion of 2-heptadecanol to its bromide. It has been pointed out in a previous paper (3) of this series that the use of secondary halides for synthesis of pure compounds is undesirable. The previous sample of 3-methyloctadecanoic acid was purified with great difficulty, and the best sample was reported as melting at 48.5–49°. The sample prepared in the present work, by methods utilizing no secondary halides, was purified with ease and melted at 50.8–51.3°. The sequence of reactions used was the following:

$$(CH_3)_2Cd + C_{15}H_{31}\overset{\overset{O}{\|}}{C}Cl \rightarrow C_{15}H_{31}\underset{\underset{O}{\|}}{C}CH_3 \xrightarrow[BrCH_2CO_2C_2H_5]{Zn}$$

I

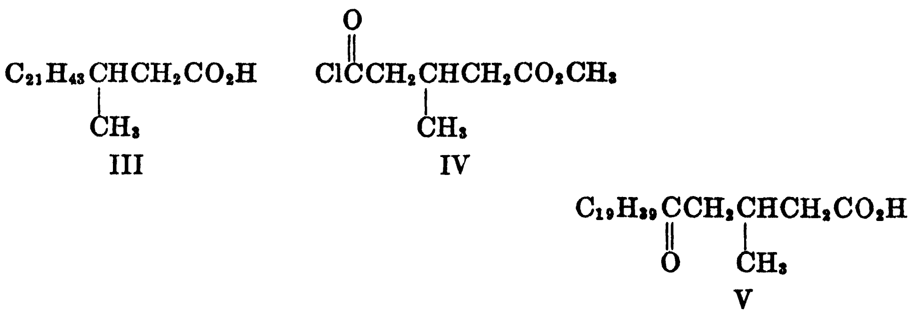
$$C_{15}H_{31}\overset{OH}{\underset{CH_3}{C}}CH_2CO_2C_2H_5 \xrightarrow[\substack{(2)\ H_2,\ Pt \\ (3)\ H_2O,\ OH^-}]{(1)\ I_2,\ heat} C_{15}H_{31}\underset{CH_3}{CH}CH_2CO_2H$$

II

The yields at all steps were reasonably good.

3-Methyltetracosanoic acid was prepared from the acid chloride (IV) of methyl hydrogen β-methylglutarate, a very convenient starting material intro-

duced by Ställberg-Stenhagen (4) for preparation of either racemic or optically active branched-chain acids. This starting material was also used for the previous preparation (5) of 3-methyltetracosanoic acid, proceeding by way of a multistep process, involving acylation and alkylation of β-keto esters to 3-methyl-5-ketotetracosanoic acid (V).

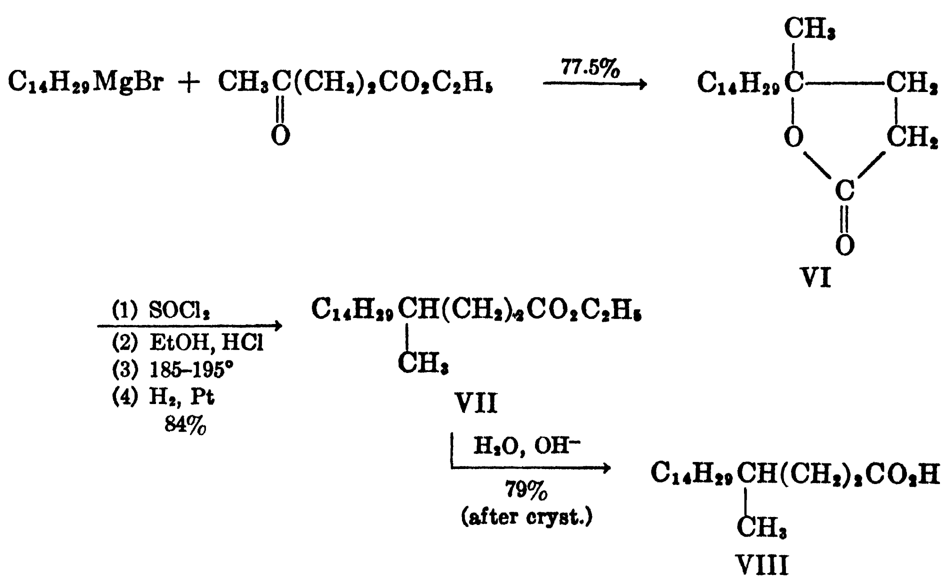


III IV V

In the present work, the ester of keto acid, V, was obtained in one step in 80% yield by reaction of the acid chloride, IV, with the cadmium reagent from *n*-nonadecyl bromide. Wolff-Kishner reduction of this keto ester yielded the desired branched-chain acid, III.

n-Pentacosanoic acid, needed for the investigation reported in the next paper, was prepared by a similar sequence of reactions, starting with the ester acid chloride of pimelic acid and the cadmium reagent from *n*-octadecyl bromide.

4-Methyloctadecanoic acid (VIII) was prepared by a method previously used (3, 6) for making 4-methyl acids or alcohols of lower molecular weight. The process was found equally effective with *n*-tetradecyl bromide as starting material, as indicated in the following equations.



The yields are comparable with those previously obtained. In the low-pressure hydrogenation to give ester, VII, the hydrogen absorption was equal to theory, within the limits of accuracy of the equipment used; nevertheless, after five crystallizations of acid VIII from acetone, the product (m.p. 51.2–51.6°; theoretical equivalent weight) gave a weakly positive Baeyer's test for unsaturation. Neither the melting point nor the unsaturation test could be altered by further crystallization. After rehydrogenation in glacial acetic acid (with no appreciable drop in pressure) and recrystallization, the acid melted at 52.6–52.8° and gave a negative test for unsaturation. Apparently, traces of unsaturated acid were carried along in solid solution or in mixed crystals.

2,3-Dimethyloctadecanoic acid (IX) was prepared from 2-heptadecanone and ethyl α-bromopropionate *via* the Reformatsky reaction, by a sequence of reactions similar to that outlined for preparation of acid, II.

$$\begin{array}{l} C_{15}H_{31}\underset{\displaystyle H_3C}{\underset{|}{C}}H\underset{\displaystyle CH_3}{\underset{|}{C}}HCO_2H \end{array}$$

IX

The yield in this Reformatsky reaction was very poor, however, even with a large excess of zinc and bromo ester, and the over-all yield of acid IX was only 9%, in contrast with the 45% over-all yield of acid II. For preparation of larger amounts of this acid, required for other work, different methods of synthesis are being investigated. The synthetic 2,3-dimethyloctadecanoic acid consists of a mixture of two racemic forms. One of these, m.p. 63.4–64.4°, was easily isolated by recrystallization of the synthetic mixture from acetone.

EXPERIMENTAL

Microanalyses by C. W. Koch and V. H. Tashinian. All melting points are corrected, all boiling points are uncorrected. All distillations, unless otherwise specified, were through a half-meter Podbielniak type column with heated jacket and partial reflux head.

2-Methyloctadecanoic acid was prepared essentially as described by Schneider and Spielman (1). Similar yields were obtained with hexadecyl bromide or hexadecyl iodide. After several crystallizations from acetone the constant m.p. 54.6–55.1° was reached (S. and S., 54.5°).

The *amide* was prepared by the method used for others described in this paper, as follows. A mixture of 10 g. of acid and 8 g. (2 mole equivs.) of thionyl chloride was heated under reflux until gas evolution had ceased (1–2 hours), then excess thionyl chloride was removed *in vacuo*. The residual acid chloride, dissolved in dry, purified dioxane, was added dropwise to a stirred solution of ice-cold concentrated aqueous ammonium hydroxide. The white, crystalline amide precipitated in nearly quantitative yield. After four crystallizations from methanol, *2-methyloctadecanamide* had the constant m.p. 105.3–105.7° (S. and S. 104.5°).

The *tribromoanilide* was prepared as previously described (7), except that the acid chloride was made with thionyl chloride; yield, after one crystallization from ethanol, 81%, m.p. 101–103°. After four more crystallizations, the constant m.p. 117.2–117.3° was reached.

Anal. Calc'd for $C_{25}H_{40}Br_3NO$: C, 49.21; H, 6.60.
Found: C, 49.56; H, 6.58.

2-Methyldocosanoic acid. The starting material for preparation of 1-bromoeicosane required for this synthesis was a commercial product (Neo-fat No. 17, Armour and Co.) described as a mixture of unsaturated C_{22} acids. A 200-g. sample of this material was esterified with 270 ml. of absolute ethanol containing 13 ml. of concentrated sulfuric acid. After dilution of the reaction mixture with water and extraction, the esters were distilled from a Claisen flask to yield 101 g. of b.p. 150–220° (2 mm.). There was a large tarry distillation residue. The distillate was hydrogenated in the presence of 20 g. of copper chromite catalyst (8), at 250° and an initial cold pressure of 4000 lbs. per sq. in (272 atmos.). Hydrogenation was complete in 90 minutes, and the pressure drop corresponded to consumption of 6.5 moles of hydrogen per mole of ester (calculated as C_{22}). The resultant mixture of solid alcohols was distilled from a Claisen flask, b.p. 158–210° (2 mm.), wt. 96.1 g. The alcohol mixture was treated with anhydrous hydrogen bromide by the usual method (9) and the bromides distilled through the column. The following fractions were obtained:

FRACTION NO	PRESSURE, MM. HG	B.P., °C.	WEIGHT G.
1	2.0	150–172	5.9
2	2.0	172–174	12.0
3	2.2	174–187	10.7
4	2.2	188–190	13.5
5	2.2	190–203	5.2
6	2.2	203–205	20.8
7	2.2	205–223	3.3
8	2.2	223–225	14.1
Residue	—	—	2.4

Since Fraction 6 is eicosyl bromide (*cf.* below), Fractions 2, 4, and 8 must be respectively hexadecyl, octadecyl, and docosyl bromides. Thus, Neo-fat No. 17 appears an excellent source of a variety of bromides, although not a high yield source of any one bromide.

Fraction 6 was redistilled and a center cut of 13.6 g. of crystalline eicosyl bromide used for preparation of 2-methyldocosanoic acid. After purification of the acid by distillation of its methyl ester and three crystallizations from acetone, the m.p. was 66.7–66.9° (S. and S. 67–67.5°); equiv. wt. 354.7 (Calc'd 354.6).

The *amide*, after one crystallization from methanol, reached the constant m.p. 109.4–109.8° (S. and S. 109–109.5°).

2-Heptadecanone (I). Pure palmitic acid was isolated from Armour's Neo-fat No. 1-56. A 500-g. lot was esterified with methanol and sulfuric acid, and the esters were distilled to yield 64% of methyl palmitate, b.p. 165–167° (4 mm.). There was also obtained a few per cent of methyl myristate and about 14% of methyl stearate. Palmityl chloride, prepared from the acid with thionyl chloride in 85% yield, was distilled rapidly from a Claisen flask, b.p. 165–170° (4 mm.).

A solution of dimethylcadmium in 250 ml. of benzene was prepared as has been previously described (10) from 10.3 g (0.425 atom) of magnesium and excess methyl bromide. To the stirred solution, originally at room temperature, there was added during about two minutes a solution of 65.9 g. (0.24 mole) of palmityl chloride in 75 ml. of benzene. After spontaneous reflux had ceased, heating under reflux with stirring was continued for one hour, then the mixture was worked up as has been described for keto esters (11). Distillation in a Claisen flask yielded 37 g. (61%) of crystalline distillate. Systematic recrystallization from methanol gave a total yield of 33.5 g. (55%) of pure 2-heptadecanone, m.p. 44.5–46.3°. The best sample melted at 45.0–46.5° [literature, m.p. 48° (12), 46.2–46.7° (2)].

3-Methyloctadecanoic acid (II). In a three-necked flask fitted with efficient mechanical stirrer was placed 125 ml. of dry sulfur-free toluene and 13 g. (0.2 atom) of zinc foil which

had been cut in strips, sanded lightly, and made into loose rolls. The apparatus was dried thoroughly by distillation of 25 ml. of toluene, then the mixture in the flask was kept at boiling as there was added, during one hour, a solution of 50 g. (0.3 mole) of ethyl bromoacetate and 25.5 g. (0.1 mole) of 2-heptadecanone in 100 ml. of toluene. Although the zinc had dissolved soon after addition was complete, heating under reflux with stirring was continued for an additional hour. After the organometallic complex had been decomposed with ice and dilute sulfuric acid the aqueous layer was separated and extracted with benzene. The extracts were washed with water and saturated sodium chloride solution, and solvent was removed by distillation, last traces in a vacuum The residue was heated at 190–200° with a few crystals of iodine for one hour. The unsaturated ester was rapidly distilled from a Claisen flask, b.p. 186–200° (4 mm.), weight 16.3 g. (50.5%).

Hydrogenation of the unsaturated ester at room temperature with 0.1 g. of platinum catalyst in 50 ml. of 95% ethanol was complete in about 6 minutes. Ethyl 3-methyloctadecanoate was obtained in quantitative yield, b.p. 186–188° (4 mm.) Saponification of 19.5 g. of the ester with 2 equivalents of 7% alcoholic potassium hydroxide gave a quantitative yield of crude acid, m.p. 48.6–49.8°. After one crystallization from acetone, there was obtained 15.8 g. of acid, and after two additional crystallizations, the m.p. was constant at 50.8–51.3°, equiv. wt., 298.5 (calc'd 298.5). The acid previously prepared (2) from a secondary halide was reported as melting at 48.5–49°.

The *amide*, after four crystallizations from methanol, melted at 93.6–94°.

Anal Calc'd for $C_{19}H_{39}NO$ C, 76.71; H, 13.21
Found: C, 76.59; H, 13.34

The *tribromoanilide*, after three crystallizations from 95% ethanol, formed clusters of white needles, m.p. 110.2–110.6°.

Anal. Calc'd for $C_{25}H_{40}Br_3NO$: C, 49.21; H, 6.60
Found: C, 49.38; H, 6.55.

2,3-Dimethyloctadecanoic acid (*IX*) was prepared by the procedure described for acid, II, except that in the Reformatsky reaction there was used 0.1 mole of 2-heptadecanone, 0.25 atom of zinc, and 0.5 mole of ethyl α-bromopropionate. The ethyl 2,3-dimethyloctadecanoate fraction of only 5.7 g contained some 2-heptadecanone, which was removed from the acid after saponification. This reaction is probably subject to improvement but was not further investigated, since enough of the product for present purposes had been obtained, and other methods appear more promising for larger scale production.

After one crystallization of the crude 2,3-dimethyloctadecanoic acid from acetone, there was obtained 2.4 g. of m.p. 55.2–60°. After two additional crystallizations, one racemic form was obtained, m.p. 63.0–64.0°.

Anal. Calc'd for $C_{20}H_{40}O_2$: equiv. wt., 312.5 Found: equiv. wt., 312.7.

The *amide*, prepared from the acid from mother liquors of the above crystallizations, was obtained in 92% yield, and after crystallization from methanol melted at 63–69° (sample a). After several additional crystallizations, a sample (b) melting at 90–92.8° was obtained. Analyses indicate that these samples differ only in stereoisomeric content.

Anal. Calc'd for $C_{20}H_{41}NO$: N, 4.52. Found: (sample a) N, 4.52; (sample b) N, 4.62.

n-Nonadecyl bromide. Ethyl *n*-nonadecanoate was prepared from *n*-octadecyl bromide according to the method of Ruhoff (13), except that the yield was improved by use of a simpler and more efficient esterification process. From 374.5 g. (1.12 moles) of commercial *n*-octadecyl bromide there was obtained a quantitative yield of crude *n*-nonadecanoic acid, which, after four crystallizations from benzene-acetone, melted at 67.3–67.8° [Francis and Piper (14), m.p. 68.65°]. *n-Nonadecanamide*, after four crystallizations from methanol, melted at 109.5–109.8°. Since this amide appears not to have been prepared previously, it was analyzed.

Anal. Calc'd for $C_{19}H_{39}NO$: N, 4.71. Found. N, 4.68.

The crude acid (1.12 moles) was heated under reflux for two hours with 1100 ml. (16.9 moles) of commercial absolute ethanol and 44 ml. of concentrated sulfuric acid. After dilution of the reaction mixture with 3.5 liters of water and addition of sufficient ether and benzene to dissolve the solid ester, a small amount of dark solid was removed from the two-

phase solution by suction filtration. The aqueous phase was extracted with two additional portions of benzene, then the extracts were washed with water and 5% sodium carbonate solution. About 5 g. of sodium nonadecanoate was filtered from the two-phase solution during the latter extraction. Distillation of the solvent from the extracts and distillation from a Claisen flask of the residue yielded 340 g. (93%) of white crystalline ethyl nonadecanoate, b.p. 193–199° (2 mm.). Literature (15), b.p. 166–168° (0.3 mm.).

The ester (112 g.) was hydrogenated in the presence of 15 g. of copper chromite catalyst (8) at 270° at an initial cold pressure of 2850 lbs. per sq. in (194 atmos.). Hydrogenation was complete in about 2 hours from the time shaker and heater were started. Catalyst was filtered from a solution of the product in 1 liter of benzene. Distillation from a Claisen flask yielded 93 g. (95%) of white crystalline *n*-nonadecanol, b.p. 204–217° (3 mm.), m.p. 59–61° [literature (15), m.p. 62–63°].

The bromide was prepared from 96.5 g. of the alcohol with anhydrous hydrogen bromide, following the usual procedure (9). Distillation through the column yielded 107 g. (90%) of white nonadecyl bromide, b.p. 184–186° (2.5 mm.), m.p. 37.0–38.5° [literature (16), m.p. 38–39°].

β-Methyl-γ-carbomethoxybutyryl chloride (IV). β-Methylglutaric acid was prepared by the method of Kent and McElvain (17), and converted to the anhydride, m.p. 46–47°, by the method of Ställberg-Stenhagen (4). The half ester was prepared by heating with methanol, according to the method (18) described for methyl hydrogen succinate, except that the product was distilled through the column to yield 17% of di-ester, b.p. 91.5–94° (5 mm.) and 71% of methyl hydrogen β-methylglutarate, b.p. 134–139° (4 mm.). The acid chloride (IV) was prepared with thionyl chloride (18) in 96.5% yield, b.p. 107–110° (16 mm.).

Methyl 3-methyl-5-ketotetracosanoate (ester of V). A cadmium reagent was prepared in 100 ml. of benzene, as previously described (10), from 2.4 g. (0.1 atom) of magnesium turnings and 34.7 g. (0.1 mole) of *n*-nonadecyl bromide. To this stirred mixture, at room temperature, was added in one portion a solution of 12 g. (0.067 mole) of ester acid chloride, IV, in 25 ml. of benzene. There was no appreciable evolution of heat. After the mixture had been stirred 75 minutes at room temperature it was heated under reflux for one hour. The viscous reaction mixture was treated with ice and sulfuric acid, then worked up as usual (10) for keto esters. On distillation from a Claisen flask, after a fore-run of 10 g., the crystalline keto ester was collected at 220–245° (*ca.* 0.5 mm.), wt. 22 g. (80%). From the fore-run was isolated 1.5 g. of octatriacontane (from coupling of the Grignard reagent), m.p. 80–81°.

For analysis, a sample of keto ester was crystallized four times from benzene, to give fine white crystals melting at 48.4–49.5°.

Anal. Calc'd for $C_{26}H_{50}O_3$: C, 76.04; H, 12.27.
Found: C, 76.55; H, 12.37.

3-Methyltetracosanoic acid (III). A 19.5 g. (0.048 mole) sample of distilled keto ester was reduced by the modified Wolff-Kishner procedure, as described by Huang-Minlon (19), except that the final heating period was for 5 hours at 210–215°. The cooled reaction mixture was diluted with water and acidified to give a quantitative yield of crude acid of m.p. 63–67°. This crude acid was esterified with 15 mole equivalents of commercial absolute alcohol in presence of sulfuric acid. About 1 g. of acid was removed as its salt, and the ester distilled through the column. After a fore-run of 2 g., the *ethyl 3-methyltetracosanoate* was collected at 219–222° (1.4 mm.), wt. 15.6 g. (80%, over-all).

For analysis, a sample of distilled ester was crystallized three times from acetone, m.p. 43.3–44.9°.

Anal. Calc'd for $C_{27}H_{54}O_2$: C, 78.96; H, 13.25.
Found: C, 78.71; H, 13.23.

After saponification of the ester with alcoholic potassium hydroxide, the acid was crystallized twice from acetone, m.p. 68.0–69.1°. Ställberg-Stenhagen (5) reported m.p. 68.4–68.6° for the *dl*-isomer of III.

The *amide*, after two crystallizations from methanol, melted at 95–101°, resolidified only on cooling to 92°, re-melted at 99.5–101°. This behavior is essentially identical with that reported in (5).

Ethyl 7-ketopentacosanoate was prepared by a procedure essentially the same as described for the ester of V, starting with 0.1 mole of octadecyl bromide and 0.08 mole of the ester acid chloride of pimelic acid. The yield of keto ester, b.p. 230–260° (3 mm.), was 13 g. (39%), and a large fraction which appeared to be octadecane was obtained. This relatively low yield may have been due to an error, but yields in this range have been obtained on certain other cadmium reactions which have been checked several times. About 4 g. of hexatriacontane, m.p. 75–78° was isolated from this reaction, indicating at least 17% coupling of the Grignard reagent.

For analysis, a sample of the ester was crystallized three times from benzene, to give shiny plates melting at 66.0–66.9°.

Anal. Calcd for $C_{27}H_{52}O_3$: C, 76.36; H, 12.34.
Found: C, 76.68; H, 12.12.

n-Pentacosanoic acid was obtained from the keto ester *via* Huang-Minlon reduction as described above. The acid was purified by distillation of the ester and three crystallizations from benzene-acetone, m.p. 82.6–83.2° [literature (14), m.p. 83.5°].

The *amide*, after three crystallizations from methyl ethyl ketone (Norit), consisted of fine, slightly tan crystals of m.p. 114.7–115.2°.

Anal. Calc'd for $C_{27}H_{55}NO$: N, 3.67. Found: N, 3.57.

γ-n-Tetradecyl-γ-valerolactone (VI) was prepared by the method (3, 6) described for lower molecular weight compounds. From 55.4 g. of *n*-tetradecyl bromide and 26 g. of ethyl levulinate there was obtained 41.5 g. (77.5%) of crystalline lactone, VI, b.p. 199–200° (4 mm.). For analysis, a sample was crystallized three times from methanol and once from acetone to yield fine white crystals, m.p. 45.5–46.7°.

Anal. Calc'd for $C_{19}H_{36}O_2$: C, 76.97; H, 12.24.
Found: C, 76.95; H, 11.97.

Ethyl 4-methyloctadecanoate (VII). Following a procedure slightly different from that (3) previously published, a solution of 17.8 g. of lactone, VI, and 21.3 g. (3 mole equivs.) of purified thionyl chloride in 20 ml. of dry benzene was heated under reflux for three hours. The cooled mixture was added dropwise during 15 minutes to 60 ml. of commercial absolute ethanol, and stirring was continued for an additional 15 minutes. After solvent had been completely removed, last traces in a vacuum, the residue was heated at 185–195° under the column until no more hydrogen chloride was evolved (2 hours). Distillation yielded 17.3 g. (89%) of ethyl 4-methyloctadecenoate, b.p. 163–164° (1 mm.).

The unsaturated ester (16.7 g.) was immediately hydrogenated at room temperature and low pressure with 0.25 g. of platinum catalyst in 60 ml. of 95% ethanol. Hydrogenation was complete in one hour, and distillation yielded 16.2 g. of saturated ester.

4-Methyloctadecanoic acid (VIII) was prepared by saponification of 15.2 g. of ester, VII. After one crystallization from acetone, there was obtained 9.6 g. of white crystals melting at 47.6–50.1°. After four more crystallizations, the m.p. remained constant at 51.2–51.6°. The acid prepared in another run reached the constant m.p. 52.2–52.4°. Both samples gave a weakly positive Baeyer's test for unsaturation. A 4.8 g. sample was rehydrogenated in 60 ml. of glacial acetic acid, with 50 mg. of platinum catalyst, for two hours. Dilution with water gave a quantitative recovery of crude acid, and after four crystallizations from acetone this sample melted at 52.6–52.8° and gave a negative Baeyer's test.

Anal. Calc'd for $C_{19}H_{38}O_2$: C, 76.45; H, 12.83; equiv. wt., 298.5.
Found: C, 76.39; H, 12.94; equiv. wt., 298.2.

The *amide*, after four crystallizations from methanol, melted at 79.7–80.2°.

Anal. Calc'd for $C_{19}H_{39}NO$: C, 76.71; H, 13.21.
Found: C, 76.83; H, 12.99.

The *tribromoanilide*, after five crystallizations from 95% ethanol, separated as nodules of small, white crystals, m.p. 95.3–99.3°. A sample placed in a bath at 97.2° melted at 97.2–97.6°.

Anal. Calc'd for $C_{25}H_{40}Br_3NO$: C, 49.21; H, 6.60.
Found: C, 49.12; H, 6.71.

SUMMARY

Several fatty acids with branching methyl groups near carboxyl have been prepared. Of this group, those which have not been previously reported are 4-methyloctadecanoic acid and 2,3-dimethyloctadecanoic acid.

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BRANCHED-CHAIN FATTY ACIDS. XI. LOCATION OF BRANCHING METHYL GROUPS NEAR CARBOXYL BY RATE STUDIES OF AMIDE HYDROLYSIS

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The location of branching groups in aliphatic hydrocarbon chains has remained a rather difficult problem, although there have recently been developed methods which are quite effective in some instances. Infra-red spectroscopy (1), X-ray diffraction (2), and monolayer studies (3) have been applied effectively, and phase diagrams between branched and straight-chain acids have been used to great advantage (4) in locating branching groups near the tail end of an acid chain. In some favorable examples, oxidative cleavage of the chain has been of value. The 10-methyl group (5) in tuberculostearic acid was first located in this manner, but a similar oxidation (6) of phthioic acid supplied only limited information. Any methods which can be applied to aliphatic acids are of considerable general utility, since acids are often obtained as degradation products in instances where the carboxyl group was not originally present in the molecule under investigation.

Since aliphatic amides containing an α-methyl group and a second large α-alkyl group have, thus far, resisted all efforts (7) to hydrolyze them to the corresponding acids, it would seem entirely possible that a single methyl substituent would have an observable effect on the rate of hydrolysis of an amide. The amide should be an ideal derivative for such a study, for it is nearly always crystalline, hence suitable for careful purification, and may usually be obtained in nearly quantitative yield (8) from the acid. Furthermore, the acid is quantitatively recovered if hydrolysis is carried to completion, an important consideration for study of natural products. Rate of hydrolysis may be easily followed by determination of ammonia evolved.

A survey of the literature has failed to reveal anything of interest concerning the hydrolysis of branched-chain amides; however, there have been reported pertinent investigations of ester hydrolysis in the presence of alkali. Of the several reports, those of Levenson and Smith (9) and of Evans, Gordon, and Watson (10) appear most authoritative, since the results in these two investigations are not only self-consistent but reasonably consistent with each other. The work of Bryant and Smith (11) is also of interest, but is handicapped by their use of commercial esters without purification. The work of these investigators shows that (a) the rate of hydrolysis of ethyl esters of normal acids remains constant in the molecular weight range from butyric to lauric acid, hence, presumably, for all higher molecular weights; (b) a substituent methyl group in the *alpha* or *beta* position decreases the rate to about one-fourth the value for a straight-chain ester; (c) a methyl substituent in the *gamma* position does not affect the rate. Since the branched-chain esters investigated were of acids con-

taining six or less carbons, the relative effect of an *alpha* or *beta* methyl was obscured by the large effect of varying the size of the second *alpha* substituent. For example, the ethyl ester of dimethylacetic acid hydrolyzes at about fifty times the rate of the ethyl ester of diethylacetic acid, although ethyl caproate hydrolyzes more rapidly than ethyl dimethylacetate. Ethyl β-methylbutyrate hydrolyzed slightly more rapidly than did ethyl α-methylbutyrate.

The results summarized above indicate that rate of amide hydrolysis should be quite effective in detecting the presence of a methyl substituent in the *alpha* or *beta* positions of higher-molecular-weight acids. The work described in the present paper, using the pure branched-chain amides whose synthesis has been reported (8), shows that these expectations may be realized. In fact, it is also possible to determine whether the substituent is *alpha* or *beta*, for the β-methyl amide hydrolyzes *more slowly* than does the α-methyl amide, in spite of the fact that the γ-methyl amide hydrolyzes at the same rate as a normal amide. This somewhat surprising result is entirely inconsistent with the suggestion of Evans, Gordon, and Watson that the effect of alkyl substituents in retarding rate of hydrolysis should be ascribed to the electron-repelling tendency of alkyl, which makes the carbonyl carbon less positive. A similar explanation has been offered by Gordon, Miller, and Day (12) for the effect of an alkyl substituent in decreasing the rate of ammonolysis of esters. It seems difficult to explain how any inductive effect of the alkyl substituent could be greater in the *beta* position than in the *alpha* position, for it is well established that inductive effects in aliphatic molecules fall off very rapidly with distance. It is still more difficult to explain how the effect could abruptly drop to zero in the *gamma* position.

These facts may be correlated if an alternative explanation is adopted, namely, that the retarding effect of an alkyl substituent on hydrolysis is largely or entirely steric in nature. If scale (Fisher-Hirschfelder) molecular models are constructed for the α-, β-, and γ-methyl amides it is apparent that the β-methyl offers more interference with the free rotation of the amide group than does the α-methyl, whereas the γ-methyl presents no interference to this rotation. These facts are reflected in the rates of hydrolysis of these amides; however, it should be emphasized that this interpretation is a qualitative one. If there is assumed a random distribution of the groups in all possible positions resulting from rotation about the valences, it is not immediately apparent why the hindering effect of the α- and β-methyl groups is as large as that observed. If, however, the attack of hydroxyl on the carbonyl carbon should be of the "face-centered" type, similar to that involved in substitutions leading to Walden inversion, then the amount of hindrance observed seems not unreasonable. Evidence for operation of this type of hindrance in substitution reactions has been presented and discussed by Bartlett and Rosen (13).

As regards the application of these observations to structure determination, it has also been found that an α,β-dimethyl amide hydrolyzes much more slowly than an amide with a methyl in either of these positions. It has been confirmed that the rates at this molecular weight level are independent of molecular weight. Straight-chain amides with 18, 19, or 25 carbons gave the same rates of hydrol-

ysis, as did α-methyl amides with 19 or 23 carbons, and β-methyl amides with 19 or 25 carbons. The apparent rate constants, illustrating these facts, are found in Table II. The variation of rate of hydrolysis with structure is graphically illustrated in Figure 2.

In a previous communication (14) it has been pointed out that if phthioic acid (6), the biologically active branched-chain acid from tubercle bacillus, is a long chain with several branching methyl groups, then two of these groups are probably in the *alpha* and *beta* positions. By use of the amide hydrolysis method, it should be possible to settle this point quickly. The rate data should fit one of the curves in Figure 2, unless the material is either non-homogeneous, or there is a larger group or ring at the *alpha* or *beta* (or possibly *gamma*) position. We are, at present, attempting the isolation of phthioic acid for such experiments.

So far as concerns the phthioic acid problem, there is no interest in acids with two methyl groups on the *alpha* or *beta* carbon, for the high optical rotation of phthioic acid cannot be reconciled with such a structure. It is planned, however, to extend the generality of the method by studying the hydrolysis of amides bearing two methyls on one carbon, and those having larger alkyl substituents.

METHOD AND CALCULATIONS

Materials. The preparation of all the amides used has been described (8), except for stearamide, which was prepared from stearic acid purified by distillation of the ester and recrystallization of the acid.

Discussion of method. A relatively concentrated solution was found most convenient and sufficiently accurate for our purposes. Hydrolysis with 0.25 N potassium hydroxide in boiling ethanol was found to be inconveniently slow; so the rate was increased to a convenient value by use of 0.5 N potassium hydroxide in boiling 1-propanol. This permitted a precision of about 5% in determination of the rate constant, except for the faster rates of the normal and 4-methyl amides, where the precision is about 10%. These limits of precision are adequate for present distinctions. If finer distinctions become necessary (for example, in investigating possible differences between normal and 4-methyl amides) the accuracy may be increased by use of more dilute solutions and the lower temperature of boiling ethanol. A principal reason for the lower accuracy for the faster rates is that the time elapsing during distillation (*cf.* Procedure) is a relatively large percentage of the total time, and the boiling point is raised slightly during this period, by concentration of the solution.

It was found that the rate constant was increased appreciably when the sample size was reduced by one-half, and it was suggested by Professor R. E. Connick, of this Laboratory, that this might be caused by a decrease in the amount of paraffin-like material (the amide or salt of the acid) in solution. At the concentrations used by us (0.035–0.07 molar), this might change the nature of the solvent sufficiently to affect the activity of the hydroxide ion. This appears to be the case, for when 0.035 molar concentration of amide and 0.035 molar concentration of n-hexadecane were used, the rate was the same as when 0.07 molar concentration of amide was used. These facts are illustrated by curves I and II, Figure 2, and by the data on 2-methyloctadecanamide, Table II.

For a set of runs made consecutively with the same normality of alkali and the same size of sample, the type of structure may be most easily determined by a simple plot of time against per cent of amide hydrolyzed, as in Figure 2. Also, this is probably the most accurate method of comparison; however, it is subject to some difficulties, especially since the normality of alcoholic potassium hydroxide changes rapidly on standing. For this reason, our most complete comparisons are on the basis of apparent rate constants (Table II), ex-

pressed in liters $moles^{-1}$ $hours^{-1}$. In Figure 2, the excessive slope of the curves (especially V) between zero and the first point indicates an irregularity at the beginning of the hydrolysis; however, this is no disadvantage if the zero time point is not used in the plots (as in Figure 3) for determination of rate constants. The remaining points gave a satisfactory straight line plot, in all cases.

A few runs were carried to completion, and the total ammonia titrated checked the theoretical amount with an accuracy of 2% or better. Several runs were made on 0.1-g. samples

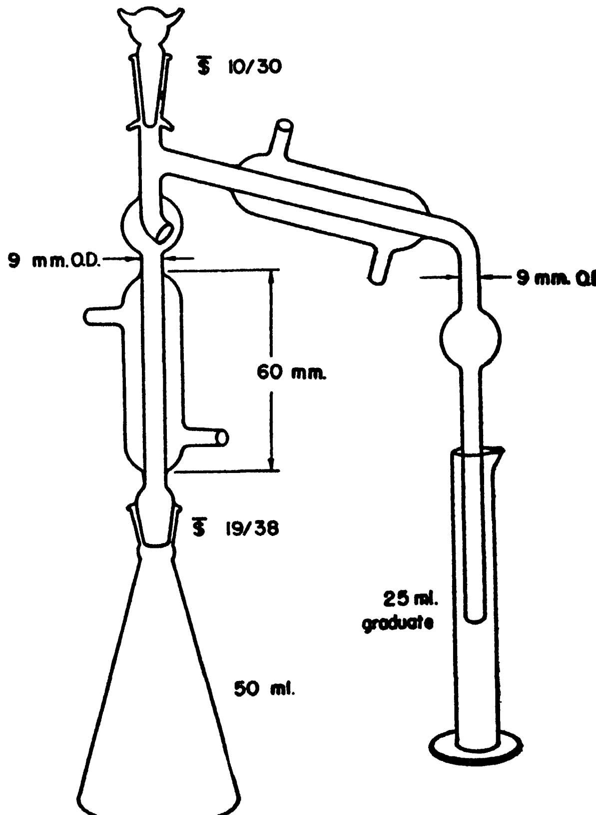

Fig. 1. Apparatus for Amide Hydrolysis

with sufficient accuracy to distinguish the type of amide, but the plot for determination of rate constant was rather inaccurate.

Procedure. The simple apparatus shown in Figure 1 was used. For a run, the sample (0.25–0.5 g.) of amide was weighed accurately into the flask, and 25 ml. of standardized, approximately 0.5 *N* potassium hydroxide in 1-propanol was pipetted into the flask. In the graduated cylinder was placed 10 ml. of 2% aqueous boric acid solution. The mixture in the flask was then heated under reflux on a hot plate, with water circulating through the upright condenser. When a determination was to be made, water was drained from the upright condenser and 10 ml. of alcohol was distilled rapidly (6–10 mins.) in order to carry over all ammonia. Time was taken at the point when distillation was stopped by running water through the upright condenser, and 10 ml. of 1-propanol was immediately added through the ground joint at the top. The graduate was lowered for the last 2 ml. of distillate and the outside of the delivery tube was rinsed with carbon dioxide-free water. A fresh sample of boric acid was then arranged to receive ammonia.

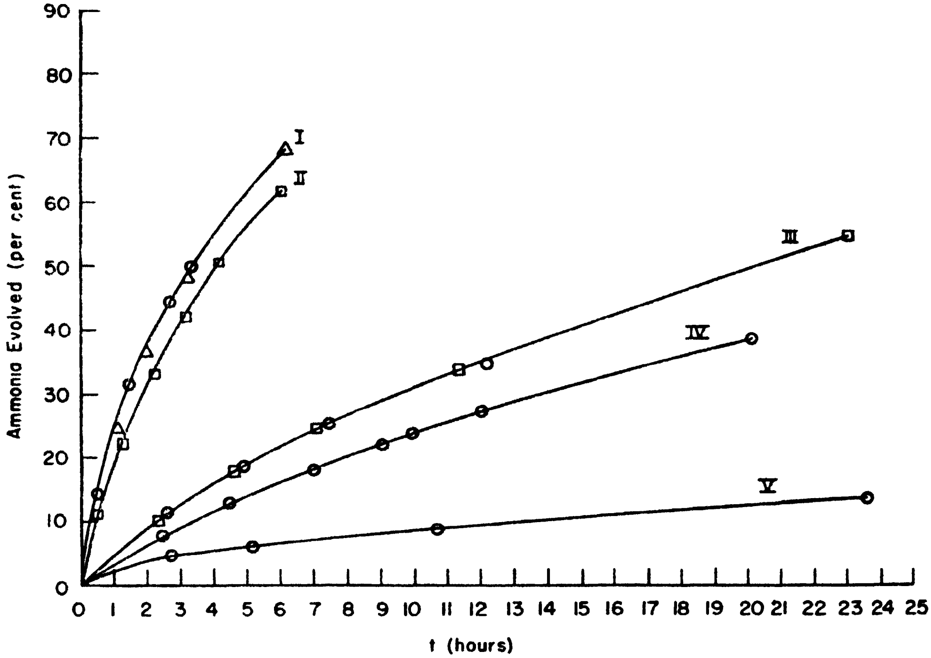

Fig 2. Rate of Hydrolysis of Amides in Approximately 0.5 N KOH in 1-Propanol. Curve I: △—△, 0.035 molar stearamide; ⊙—⊙, 0.034 molar 4-methyloctadecanamide. Curve II: ⊡—⊡, 0.071 molar stearamide. Curve III: ⊡—⊡, 0.034 molar 2-methyldocosanamide; ⊙—⊙, 0.034 molar 2-methyloctadecanamide. Curve IV: 0.034 molar 3-methyltetracosanamide. Curve V: 0.031 molar 2,3-dimethyloctadecanamide.

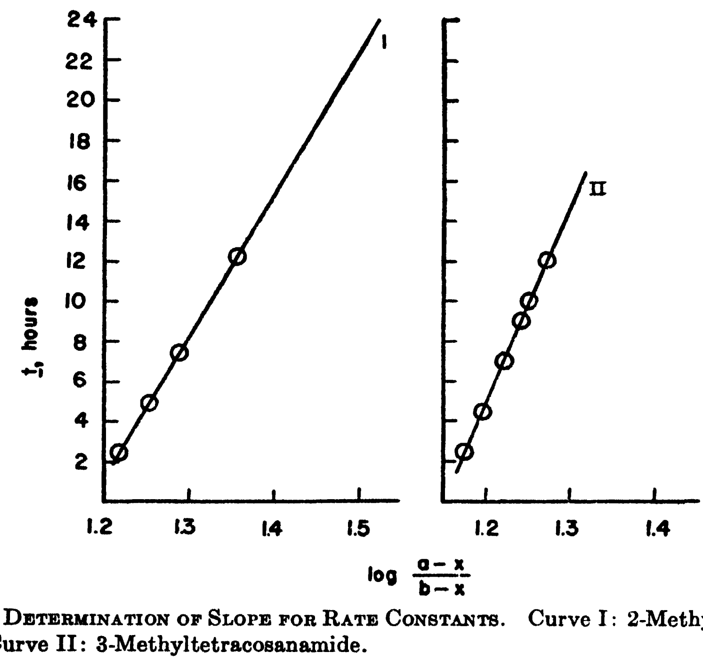

Fig. 3. Determination of Slope for Rate Constants. Curve I: 2-Methyloctadecanamide. Curve II: 3-Methyltetracosanamide.

The distillate was rinsed into a 125-ml. Erlenmeyer flask with 25 ml. of carbon dioxide-free water, and the ammonia was titrated directly with 0.02 N hydrochloric acid, using the excellent Tetrabromophenol Blue and Methyl Red indicator of Stover and Sandin (15). A blank titration was made and subtracted, according to the method of these authors.

The time interval at which titrations were made was adjusted to the rate of the hydrolysis being studied. For normal or 4-methyl amides, titrations were made at intervals o

TABLE 1

CALCULATIONS FOR RATE CONSTANTS, 2-METHYLOCTADECANAMIDE

t (HRS.)	x	$a-x$	$b-x$	$\log \frac{a-x}{b-x}$
2.58	0.0038	0.494	0.0298	1.219
4.90	.0063	.492	.0273	1.256
7.48	.0086	.489	.0250	1.291
12.22	.0123	.486	.0213	1.358

$a = 0.4984$

$$\text{slope} = \frac{24.0 - 4.6}{1.525 - 1.250} = 70.6$$

$b = 0.0336$

$$K = \frac{2.303}{(0.4648)\ (70.6)} = 0.070.$$

3-METHYLTETRACOSANAMIDE

t (HRS.)	x	$a-x$	$b-x$	$\log \frac{a-x}{b-x}$
2.50	0.0027	0.4728	0.0316	1.175
4.50	.0045	.4710	.0298	1.199
6.98	.0062	.4693	.0281	1.223
9.05	.0077	.4678	.0266	1.245
9.98	.0082	.4673	.0261	1.253
12.05	.0094	.4661	.0249	1.272

$a = 0.4755$

$$\text{slope} = \frac{15.0 - 5.0}{1.303 - 1.202} = 99.0$$

$b = 0.0343$

$$K = \frac{2.303}{(0.4412)\ (99.0)} = 0.0527.$$

30–60 minutes; for the slower hydrolyses, samples were taken at intervals of 1–4 hours. Four to six titrations were commonly made. The amount of boric acid used will absorb about 9 mg. of nitrogen quantitatively (15).

All 1-propanol used was a distilled commercial grade, b.p. 94–99°. The potassium hydroxide solution was standardized each day that it was used. The normality changed about 0.0005 units per day.

Calculation of rate constants. The second order apparent rate constant, k, for the temperature of the boiling solution was calculated from the equation:

$$t = \frac{2.303}{k(a-b)}\left(\log \frac{b}{a} + \log \frac{a-x}{b-x}\right)$$

where a is the initial molarity of alkali, b is the initial molarity of amide, and x is the moles reacted in time, t. By plotting $\log \frac{a-x}{b-x}$ against t in hours, the equation was reduced to the form:

$$k = \frac{2.303}{a-b}\left(\frac{1}{\text{slope}}\right)$$

The plot gave a satisfactory straight line for points taken up to the half time of the reaction. The points naturally became less reliable, as x approached b. It was felt that our accuracy is not such, nor our times sufficiently long, to justify a "glass correction," as used by Levenson and Smith (9).

TABLE II

APPARENT RATE CONSTANTS FOR SAPONIFICATION OF AMIDES

AMIDE	0.067 MOLAR[a] AMIDE	0.034 MOLAR[a] AMIDE
Stearic	0.34	0.38
Nonadecanoic		.35
Pentacosanoic		.34
4-Methyloctadecanoic	.39	.40
2-Methyloctadecanoic	.058	.070
	.054	
		.054[b]
2-Methyldocosanoic	.059	.074
3-Methyloctadecanoic	.045	
3-Methyltetracosanoic		.053
2,3-Dimethyloctadecanoic		.013

[a] These figures represent the approximate molarity of amide, and in all runs the potassium hydroxide in 1-propanol was approximately 0.5 molar. Exact molarities were used for the calculations. The temperature is that of the boiling solution, about 99°.

[b] In this run, 0.034 molar concentration of n-hexadecane was added to the saponification mixture. Similar effects were observed in several runs with stearamide, but the data are less convincing on account of the lower accuracy for the faster hydrolyses.

Sample plots are shown in Figure 3, and in Table I are the calculated values from which the plots for 2-methyloctadecanamide and 3-methyltetracosanamide were made. Rate constants, k, are in liters moles^{-1} hours^{-1}. Data for the other amides were treated in a similar manner.

SUMMARY

It has been shown that the rate of amide hydrolysis is a convenient and rapid method for distinguishing between an α-methyl, a β-methyl, and an α,β-dimethyl amide. The rate for each of these is different, and all are slower than that for a normal or γ-methyl amide.

Since the β-methyl amide is hydrolyzed more slowly than the α-methyl amide, the retarding effect of the alkyl substituents is attributed to steric hindrance.

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[COMMUNICATION NO. 1218 FROM THE KODAK RESEARCH LABORATORIES]

THE CHEMISTRY OF *o*-TERPHENYL. III. SULFONIC ACIDS

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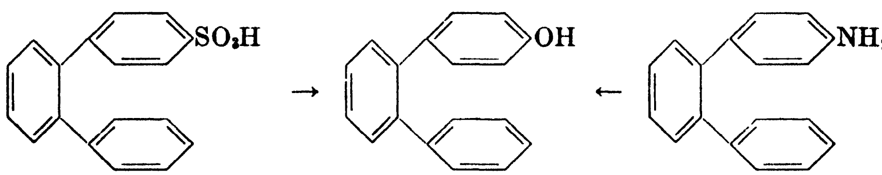
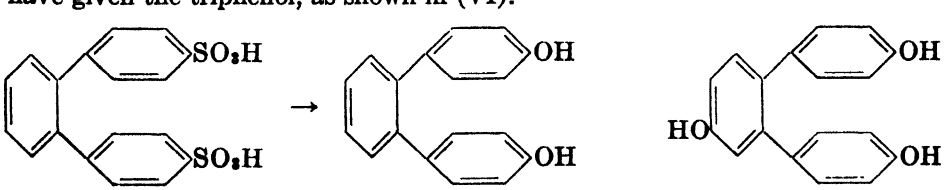
In previous papers (1, 2, 3) the chemical behavior of *o*-terphenyl with all the common reagents except sulfuric acid has been described. In this communication an account is given of several sulfonic acids which contain the *o*-terphenyl nucleus.

Mono-, di-, and tri-sulfonic acids have been obtained by direct sulfonation of the hydrocarbon; however, the mono-derivative was formed in very low yield. A more satisfactory method for the preparation of *o*-terphenyl-4-sulfonic acid (I) was by treatment of the hydrocarbon with one equivalent of chlorosulfonic acid. The position of the sulfonic acid group was shown by converting it into 4-hydroxy-*o*-terphenyl (II), which was synthesized from 4-amino-*o*-terphenyl (III) by the Sandmeyer reaction. The sulfonic acid was converted to a triphenylguanidine salt and to the sulfonamide.



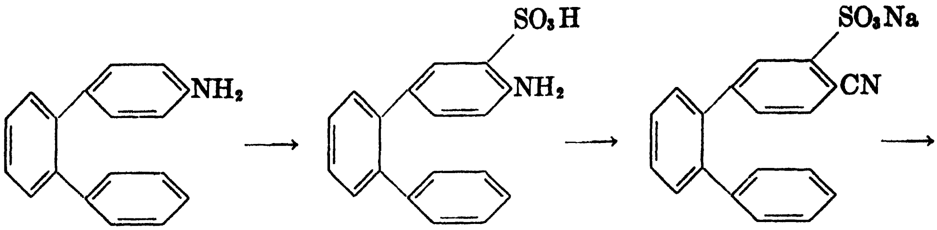
I II III

The di- and tri-sulfonic acids were readily obtained by direct sulfonation of the hydrocarbon, with slight changes in acid concentration, time, and temperature. These sulfonic acids were converted in good yield to the corresponding phenols by alkaline fusion. The disulfonic acid (IV) gave the known (4) 4,4″-dihydroxy-*o*-terphenyl (V), thus locating the positions of the sulfonic acid groups. The position of the third acidic radical in the trisulfonic acid has not been determined conclusively. The trihydroxy-*o*-terphenyl formed from it by alkaline fusion is a very weak coupler by photographic tests (5), which observation probably indicates coupling in an *ortho* position; if there were an unoccupied *para* position, the substance would be expected to be a strong coupler. In view of the behavior of *o*-terphenyl on polybromination (2), the third sulfonic acid group in all probability entered the central ring; its replacement by hydroxyl then would have given the triphenol, as shown in (VI).

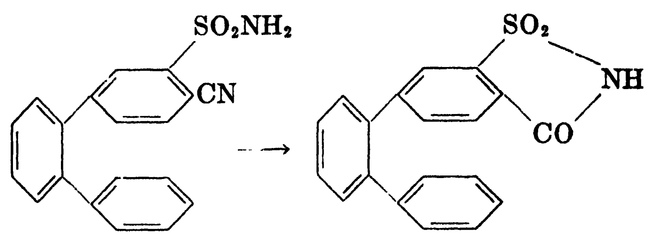


IV V VI

4-Amino-*o*-terphenyl was monosulfonated by the "bake process," which gave 4-amino-*o*-terphenyl-3-sulfonic acid (VII). For proof of structure, the acid was converted to an analog of saccharin (VIII), thus showing that the groups were *ortho* to each other. The amine (VII) gave a nitrile (IX) by the Sandmeyer reaction; this nitrile then was transformed into the cyanosulfonamide (X) by the usual reactions. Treatment of the amide with sodium hydroxide (6) gave the cyclic derivative (VIII), which, like saccharin, has a sweet taste after the initial bitterness has disappeared.

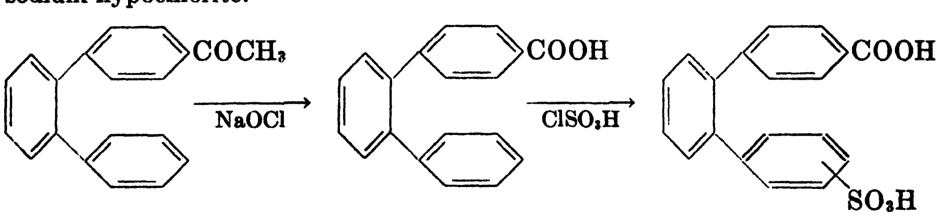


III VII IX



X VIII

4-*o*-Terphenoic acid (XI) was monosulfonated, using chlorosulfonic acid in tetrachloroethane. The resulting sulfocarboxylic acid (XII) gave x-sulfo-4-*o*-terphenoyl dichloride, when treated with phosphorus pentachloride, and the corresponding diamide by the action of ammonia on the dichloride. The 4-*o*-terphenoic acid (XI) was prepared in quantity from 4-acetyl-*o*-terphenyl and sodium hypochlorite.



XI XII

EXPERIMENTAL

Sodium o-terphenyl-4-sulfonate (I). A solution of 200 g. (0.87 mole) of Santowax O[1] in 600 ml. of dry chloroform was cooled to 10°, and a solution of 110 g. (0.94 mole) of freshly distilled chlorosulfonic acid was added dropwise, with stirring. The solution then was allowed to warm up to room temperature, and finally heated at 50° for four hours. Water (*ca.* 800 ml.) was added to the cold reaction mixture, and the chloroform removed at re-

duced pressure. The aqueous solution was filtered, neutralized with 750 ml. of a 5% solution of sodium hydroxide, and cooled in an ice-bath. The precipitated sodium salt was filtered and washed with a half-saturated brine solution. The crude salt was recrystallized from 1600 ml. of boiling water to give 234 g. (81%) of white platelets. A sample was recrystallized again from water for analysis.

Anal. Calc'd for $C_{18}H_{13}NaO_3S$: C, 65.0; H, 3.9.
Found: C, 64.5; H, 4.2.

The *1,2,3-triphenylguanidine salt* was prepared from an aqueous solution of the free acid. After two recrystallizations from aqueous methanol (1:3), the salt melted at 239.5–241°.

Anal. Calc'd for $C_{37}H_{31}N_3O_3S$: C, 74.4; H, 5.2.
Found: C, 74.4; H, 5.3.

The *sulfonamide* was prepared from the sodium salt, and recrystallized from benzene; m.p. 182–183°.

Anal. Calc'd for $C_{18}H_{15}NO_2S$: N, 4.5. Found: N, 4.5.

Potassium o-terphenyl-4,4"-disulfonate (IV). A solution of 23 g. (0.1 mole) of Santowax O and 60 g. of concentrated sulfuric acid was heated on the steam-bath for four hours, then cooled and poured upon ice. Sufficient potassium chloride was added to form a 20% solution, and the mixture was stirred for two hours. The precipitated sulfonate salt was removed, washed with a little potassium chloride solution, and recrystallized from 150 ml. of hot water. After a second recrystallization from 100 ml. of water, 23.6 g. (51%) of white glistening plates were obtained. A sample was again recrystallized for analysis.

Anal. Calc'd for $C_{18}H_{12}K_2O_6S_2$: C, 46.3; H, 2.6.
Found: C, 46.2; H, 3.1.

Potassium o-terphenyl-4,4',4''-trisulfonate. A mixture of 115 g. (0.5 mole) of Santowax O and 750 g. of 100% sulfuric acid was heated at 110° (oil-bath temperature) for one and one-half hours. The solution was cooled, and poured upon 2 kg. of ice. After the addition of 480 g. of potassium chloride, the sulfonate salt precipitated. The mixture was cooled in ice, filtered, and washed with cold 20% potassium chloride solution. The crude salt was recrystallized once from 550 ml. of hot water, and twice more using the minimum amount of water. The filter cake was washed with methanol to remove any remaining free acid. The yield of thrice-recrystallized potassium salt dihydrate was 173 g. (54%). A sample was recrystallized once more for analysis.

Anal. Calc'd for $C_{18}H_{11}K_3O_9S_3 + 2H_2O$: C, 34.8; H, 2.4.
Found: C, 34.5; H, 2.1.

4-Hydroxy-o-terphenyl (II). (a) *From sodium o-terphenyl-4-sulfonate.* A mixture of 240 g. of potassium hydroxide and 10 ml. of water was heated to 250° in a nickel crucible, and 120 g. of powdered sodium *o*-terphenyl-4-sulfonate was added gradually. The melt was heated at 250–280° for one-half hour, and then at 310° for five minutes. The reaction mixture was allowed to cool somewhat, and the tarry solid was transferred to 1200 ml. of ice-water, in which it gradually dissolved. The solution was acidified with hydrochloric acid, precipitating the hydroxy compound as a tar which gradually became crystalline. After filtration, the crude product was dissolved in 750 ml. of 2% aqueous sodium hydroxide, filtered, and reprecipitated with acetic acid to give 78 g. (88%) of material melting at 119–126°. Recrystallization from 600 ml. of carbon tetrachloride gave 60 g. (67.6%) of 4-hydroxy-*o*-terphenyl, m p. 127.5–128.5°. A sample, recrystallized twice more for analysis, melted at 129–130°.

Anal. Calc'd for $C_{18}H_{14}O$: C, 87.8; H, 5.7.
Found: C, 87.4; H, 6.0.

(b) *From 4-amino-o-terphenyl.* A mixture of 2.45 g. (0.01 mole) of 4-amino-*o*-terphenyl, 100 ml. of water, and 8.5 ml. of 6 *N* hydrochloric acid was heated on the steam-bath until solution was complete. Cooling caused fine needles of the hydrochloride to separate. The mixture was cooled to 0°, and then a solution of 0.70 g. of sodium nitrite in 5 ml. of water was added dropwise, with stirring. Stirring was continued for fifteen minutes after

the addition; then, the cold solution was dropped through a steam-filled tube into boiling water. The orange-red tar which formed was dissolved in benzene, boiled with Darco, filtered, and evaporated to dryness. The residue was recrystallized twice from 10-ml. portions of carbon tetrachloride to give 0.95 g. (39%) of pale orange needles; m.p. 128–129.5°. A melting point of the mixture with a sample of 4-hydroxy-*o*-terphenyl prepared from the sulfonic acid was not depressed.

The *acetyl derivative* was prepared by refluxing a mixture of 0.5 g. of the compound, 10 ml. of acetic anhydride, and 2 g. of sodium acetate for two hours. The yield of crude product was 0.57 g.; m.p. 99–101°. Recrystallization from methanol produced fine white needles; m.p. 102–103°.

Anal. Calc'd for $C_{20}H_{16}O_2$: C, 83.3; H, 5.6.
Found: C, 83.4; H, 5.9.

4,4″-Dihydroxy-o-terphenyl (V). To a molten mixture of 24 g. of potassium hydroxide and 1 ml. of water at 250°, there was added 6 g. of potassium *o*-terphenyl-4,4″-disulfonate. The mixture was stirred at 280° for fifteen minutes, and then at 340° for five minutes. The melt was cooled, dissolved in water, and the resulting solution acidified. The gray-white product (m.p. 228–230°) was recrystallized from 75 ml. of *p*-cymene, with Darco; yield, 2 g. (59%); m.p. 230–231°. A melting point of the mixture with an authentic sample of *4,4″*-dihydroxy-*o*-terphenyl, prepared from the 4,4″-diamino compound (4), was not depressed.

The *diacetyl derivative* was prepared as described for the monohydroxy compound. After a single recrystallization from methanol, the product melted at 184.5–186.5°; this compares favorably with the value reported by Price and Mueller (186.0–186.4°) for 4,4″-diacetoxy-*o*-terphenyl.

4,4′,4″-Trihydroxy-o-terphenyl (VI). To 30 g. of molten potassium hydroxide in a nickel crucible at 250°, there was added, with stirring, 10 g. of potassium *o*-terphenyl-4,4′,4″-trisulfonate. The temperature was then increased gradually, and at 270–280° the mixture became clear. It was stirred for fifteen minutes at 290–300°, cooled somewhat, and dissolved in ice-water. The clear solution was acidified to yield 3.9 g. (89%) of crude trihydroxy compound; m.p. 233–236°. After two recrystallizations from methanol, the fine white needles melted at 237–237.5°.

Anal. Calc'd for $C_{18}H_{14}O_3$: C, 77.7; H, 5.1.
Found: C, 77.4; H, 5.2.

The *triacetyl derivative* was prepared as described for the monohydroxy compound, and recrystallized from methanol; m.p. 179–180°.

Anal. Calc'd for $C_{24}H_{20}O_6$: C, 71.2; H, 5.0.
Found: C, 70.7; H, 5.2.

Sodium 4-amino-o-terphenyl-3-sulfonate (VII). A mixture of 49 g. (0.2 mole) of 4-amino-*o*-terphenyl, 20.5 g. (0.2 mole) of 95% sulfuric acid, and 250 ml. of water was stirred for one-half hour on the steam-bath, and then evaporated to dryness. The dry salt was heated under reduced pressure (15 mm.) in an oil-bath at 190–210° for forty-eight hours. The reaction mixture was cooled, and dissolved in 500 ml. of water containing 11 g. of sodium carbonate. After treatment with Darco, the solution was evaporated to dryness, yielding 64.5 g. of the crude salt. Recrystallization from 150 ml. of hot water produced clusters of transparent needles which were washed on the filter with cold water and acetone; yield, 54.2 g. (78.2%). A sample was recrystallized twice more from water.

Anal. Calc'd for $C_{18}H_{14}NNaO_3S$: C, 62.2; H, 4.1; N, 4.0.
Found: C, 61.2; H, 4.3; N, 3.9.

Sodium 4-cyano-o-terphenyl-3-sulfonate (IX). A solution of 16.4 g. (0.047 mole) of sodium 4-amino-*o*-terphenyl-3-sulfonate and 3.8 g. (0.055 mole) of sodium nitrite in 830 ml. of water was cooled to 0°. The resulting suspension was added slowly to ice and 20 ml. of concentrated hydrochloric acid, the temperature being kept below 5°. The solution was allowed to stand for twenty minutes and the pale yellow solid was filtered and washed with ice-water. The moist diazonium salt was added in portions to a solution of cuprous

cyanide (prepared from 15 g. of sodium cyanide, 18 g. of cupric sulfate pentahydrate, and 110 ml. of water), while the temperature was maintained at 55–63°. The solution was heated at 60–80° for one hour; then 12 g. of salt was added. On cooling, the product separated as a dark brown semi-crystalline mass, which was removed, washed with cold brine, and dried. The crude product was extracted with methanol and the extract evaporated to dryness. The dark yellow solid weighed 15.3 g. (91%).

4-Cyano-o-terphenyl-3-sulfonamide (X). An intimate mixture of 7.1 g. (0.02 mole) of crude sodium 4-cyano-*o*-terphenyl-3-sulfonate and 9.3 g. (0.043 mole) of phosphorus pentachloride was heated at 140–150° for one-half hour, cooled, dissolved in warm benzene, and filtered. The benzene filtrate was washed with water, and then stirred overnight with 30 ml. of 28% ammonium hydroxide. The benzene layer was decanted and the residual yellow solid removed, washed, and dried; yield, 3.8 g.; m.p. 190–220° (dec.). After three recrystallizations from alcohol, the white crystalline product melted at 273–276°.

Anal. Calc'd for $C_{19}H_{14}N_2O_2S$: C, 68.3; H, 4.2; N, 8.4.

Found: C, 68.3; H, 4.3; N, 8.2.

4-o-Terphenoyl-3-sulfimide (VIII). To a suspension of 0.5 g. (0.0015 mole) of 4-cyano-*o*-terphenyl-3-sulfonamide in 10 ml. of water, there was added 1.5 ml. of 1 *N* sodium hydroxide, and the mixture was heated under reflux for four hours. By this time complete solution had taken place, and the odor of ammonia was no longer detectable. Upon acidification of the solution, the product separated oily, but soon crystallized, to give 0.5 g. of material of m.p. 241–247°. Recrystallization from dilute methanol brought the melting point to 244.5–247.5°, which was not altered by further recrystallization from dilute acetone.

Anal. Calc'd for $C_{19}H_{13}NO_3S$: C, 68.1; H, 3.9; N, 4.2.

Found: C, 68.2; H, 4.3; N, 4.3.

4-Acetyl-o-terphenyl. The following method, using acetyl chloride in ethylene chloride, was found to be more convenient and to give better yields than the one previously described (2). A solution of 138 g. (0.60 mole) of Santowax O[1] in 150 ml. of ethylene dichloride, and 50 g. (0.63 mole) of acetyl chloride was cooled in an ice-salt bath to below 0° and 87 g. (0.65 mole) of resublimed aluminum chloride was added in portions during one hour, while the temperature was kept below 0°.[2] Stirring was continued for two hours after the addition, and the mixture was poured into ice and concentrated hydrochloric acid. The organic layer was separated, an equal volume of water was added, and the mixture was made nearly neutral with sodium carbonate solution. The solvent was then removed by steam-distillation, the residual oil was dissolved in ether, washed with water, and filtered. The filtrate was evaporated to about 300 ml. and allowed to crystallize. The crystals were washed with ether; yield (first crop) 89 g.; m p. 93.5–94.0°. Concentration of the filtrate to 150 ml. and cooling gave an additional 12.3 g. (m.p. 92.5–93.5°) for a total yield of 101.3 g. (62.2%).

4-o-Terphenoic acid (XI). This compound was reported by Allen and Pingert (2), but no details were given. A sodium hypochlorite solution was prepared by passing 111 g. (3.13 g. atoms) of chlorine into a solution of 150 g. (3.75 moles) of sodium hydroxide in 225 ml. of water and containing 450 g. of crushed ice. The temperature was kept below 0° during the addition of chlorine by an ice-salt bath. The hypochlorite solution was added in a fine stream, with stirring, to a warm (50°) solution of 90 g. (0.33 mole) of 4-acetyl-*o*-terphenyl in 1200 ml. of methanol. Finally, the mixture was heated under reflux for five hours, cooled to about 5°, filtered, and washed with water. The solid cake was dissolved in 900 ml. of hot water, filtered, and the hot filtrate acidified with hydrochloric acid. The weight of crude acid was 75 g. By concentration of the methanolic filtrate, the yield of crude acid was increased to 90 g. Recrystallization from 1 liter of methanol,

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[1] Santowax O, containing approximately 95% *o*-terphenyl, is available commercially from the Monsanto Chemical Company.

[2] A higher temperature and a longer reaction time favor isomerization to the *m*- and *p*-terphenyl analogs (1).

with Darco, gave 68.4 g. of pure acid, m.p. 202–203°; the yield was increased to 79.4 g. (87.7%) by concentration of the filtrate to 200 ml.

The *amide* was prepared by the action of thionyl chloride followed by ammonia, on the free acid, and recrystallized twice from absolute alcohol. The rectangular, transparent plates melted at 246.5–248.5°.

Anal. Calc'd for $C_{19}H_{15}NO$: N, 5.1. Found: N, 4.9.

The *methyl ester*[3] was prepared in quantitative yield by the action of thionyl chloride followed by methanol, on the free acid. After recrystallization from methanol, the ester melted at 99.5–100.5°.

Anal. Calc'd for $C_{20}H_{16}O_2$: C, 83.3; H, 5.6.
Found: C, 83.2; H, 5.8.

x-Sulfo-4-o-terphenoic acid (XII). A solution of 27.0 g. of 4-*o*-terphenoic acid in 200 ml. of purified *s*-tetrachloroethane was cooled to about 10°, and 12 g. of redistilled chlorosulfonic acid in 25 ml. of tetrachloroethane was added dropwise. Finally, the mixture was stirred at 55–60° overnight, cooled in an ice-bath, filtered, and the product washed with cold chloroform, followed by ether. The crude yield was 23 g. (66%). Recrystallization from 500 ml. of nitroethane (or nitromethane) yielded 19.1 g. (55%) of nearly colorless plates; m.p. 243–248°.

x-Sulfo-4-o-terphenoyl dichloride. An intimate mixture of 19 g. (0.054 mole) of x-sulfo-4-*o*-terphenoic acid and 22.4 g. (0.108 mole) of phosphorus pentachloride was warmed on a steam-bath, with occasional shaking. When the reaction had subsided and the melt was homogeneous, the mixture was cooled. The solid was broken up, transferred to a beaker of ice-water, and extracted with ether. The ether solution was washed with cold water, dried over magnesium sulfate, and filtered. The solvent was removed at reduced pressure to give 13 g. (62%) of white solid (m.p. 141–149°) which could not be recrystallized from any common solvent.

Anal. Calc'd for $C_{19}H_{12}Cl_2O_3S$: C, 58.3; H, 3.1; Cl, 18.1.
Found: C, 58.6; H, 3.30; Cl, 16.1, 15.8.

The *diamide* was prepared from the dichloride by heating with ammonium carbonate and ammonia. After recrystallization from alcohol, the compound melted at 272–277°.

Anal. Calc'd for $C_{19}H_{16}N_2O_3S$. N, 8.0 Found: N, 7.7.

SUMMARY

The following sulfonated *o*-terphenyl derivatives have been prepared and described: *o*-terphenyl-4-sulfonic acid; *o*-terphenyl-4,4″-disulfonic acid; *o*-terphenyl-4,4′,4″-trisulfonic acid; 4-amino-*o*-terphenyl-3-sulfonic acid; x-sulfo-4-*o*-terphenoic acid. Related substances, also described for the first time, include 4-hydroxy-*o*-terphenyl, 4,4′,4″-trihydroxy-*o*-terphenyl, and derivatives of all the foregoing. A homolog of saccharin also has been obtained.

ROCHESTER 4, N. Y.

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[3] This substance was prepared by Roger J. Tull, formerly of these Laboratories.

[Communication No. 1219 from the Kodak Research Laboratories]

THE CHEMISTRY OF *o*-TERPHENYL. IV. AMINE DERIVATIVES

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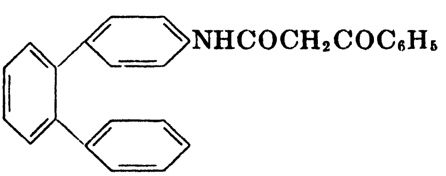
The current accessibility of *o*-terphenyl and many of its derivatives (1, 2, 3, 4, 5) has made it possible to prepare representatives of many classes of compounds containing this ring system. For instance, 4-amino-*o*-terphenyl can readily be converted to 4-benzoylacetamido- (I), 4-(2′-methoxybenzoylacetamido)- (II), and 4-(1′-hydroxy-2′-naphthoylamido)- (III) *o*-terphenyls, while 4,4″-disalicylamido-*o*-terphenyl is readily prepared from the corresponding diamine.



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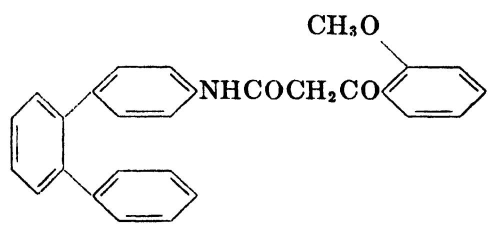
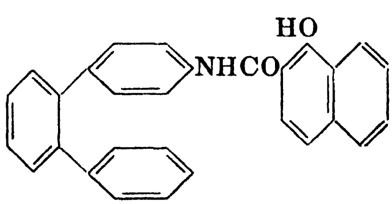


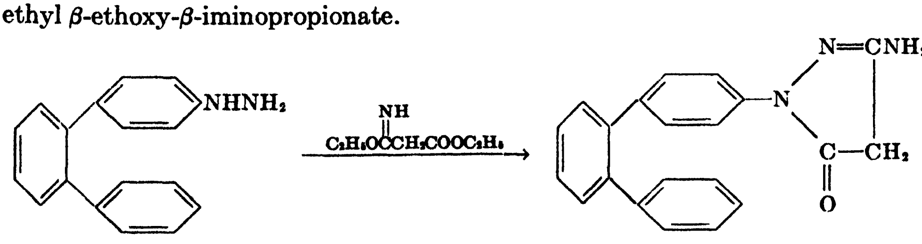
II



III

An *n*-butyl homolog of (I) was prepared from 4-*n*-butyryl-*o*-terphenyl, obtained by the Friedel-Crafts reaction; a Clemmensen reduction of the ketone gave 4-*n*-butyl-*o*-terphenyl, which was then nitrated and reduced, and the amine condensed with ethyl benzoylacetate. The position of the nitro group was not determined.

The 4-amino-*o*-terphenyl was converted into 4-hydrazino-*o*-terphenyl (IV) by the usual procedure, reduction of the diazotized amine. The hydrazine was used to prepare 1-(4-*o*-terphenylyl)-3-amino-5-pyrazolone (V) by interaction with ethyl β-ethoxy-β-iminopropionate.



IV V

EXPERIMENTAL

4-n-Butyryl-o-terphenyl. A solution of 138 g. of *o*-terphenyl, 67 g. of *n*-butyryl chloride, and 150 g. of ethylene dichloride was cooled to −10°, and 87 g. of resublimed aluminum chloride added in portions, with stirring, during one hour. The mixture was stirred for four hours at −5 to 0° and decomposed with iced hydrochloric acid. The organic layer was removed, washed with dilute acid, mixed with water, and made almost neutral with sodium carbonate solution. The solvent was removed by steam-distillation, and the residual oil extracted with 700 ml. of ether. After removal of the solvent, distillation of the crude, fluorescent oil yielded 120 g. of the ketone; b.p. 187–190° (1 mm.). It crystallized from methanol in hard, transparent prisms; m.p. 78°.

Anal. Calc'd for $C_{22}H_{20}O$: C, 87.9; H, 6.7.
Found: C, 87.6; H, 6.7.

4-n-Butyl-o-terphenyl. Amalgamated zinc was prepared by treating 250 g. of mossy zinc with 300 ml. of water, 25 g. of mercuric chloride, and 12 g. of concentrated hydrochloric acid. To the zinc amalgam thus obtained there were added 35 ml. of concentrated hydrochloric acid, 10 ml. of acetic acid, and a solution of 50 g. of 4-*n*-butyryl-*o*-terphenyl in 100 ml. of toluene. The mixture was heated under reflux for twenty-four hours; hydrogen chloride was passed in slowly during the first six hours. The toluene solution was removed, washed, and distilled. The hydrocarbon (34 g.) was collected at 165–167° (1 mm.), and crystallized from methanol in large, transparent prisms; m.p. 44°.

Anal. Calc'd for $C_{22}H_{22}$: C, 92.3; H, 7.7.
Found: C, 92.3; H, 7.7.

4-n-Butyl-x-nitro-o-terphenyl. The nitration of 8.6 g. of 4-*n*-butyl-*o*-terphenyl was carried out in the manner described for 4-nitro-*o*-terphenyl (5). Distillation of the crude product yielded 6.7 g. of yellow oil; b.p. 196–206° (1 mm.).

Anal. Calc'd for $C_{22}H_{21}NO_2$: N, 4.2. Found: N, 4.3.

x-Amino-4-n-butyl-o-terphenyl. The reduction of 4-*n*-butyl-*x*-nitro-*o*-terphenyl was carried out in the manner described for 4-amino-*o*-terphenyl (5). The product was an intractable oil which was purified by preparation of the *p*-nitrobenzanilide derivative, followed by hydrolysis.

x-p-Nitrobenzamido-4-n-butyl-o-terphenyl was prepared by adding 15 ml. of 10% sodium hydroxide solution, in portions with shaking, to a solution of 3 g. of the amine and 3 g. of *p*-nitrobenzoyl chloride in dioxane. After fifteen minutes, the solution was poured into water. The product which separated was recrystallized twice from two 200-ml. portions of ethanol; yield, 2.8 g.; m.p. 155.5°.

Anal. Calc'd for $C_{29}H_{26}N_2O_3$: N, 6.2. Found: N, 6.3.

A pure sample of the *amine* was obtained by hydrolysis of the pure *p*-nitrobenzamido derivative. This was accomplished by boiling under reflux a solution of 1.3 g. of the amide in 90 ml. of alcohol with 18 ml. of 50% sulfuric acid for about 60 hrs.

The solution was cooled, neutralized with alkali, the alcohol evaporated, and the aqueous solution extracted with ether. Removal of the ether gave an oil which crystallized from 80% alcohol as fine, colorless needles; yield, 0.5 g.; m.p. 59.5–60°.

Anal. Calc'd for $C_{22}H_{23}N$: N, 4.6. Found· N, 4.9.

4-Hydrazino-o-terphenyl (IV). The diazonium chloride of 4-amino-*o*-terphenyl was prepared at 0° from 7.4 g. of the amine, 9 ml. of concentrated hydrochloric acid, 40 ml. of water, and 2.2 g. of sodium nitrite. The resulting solution was added gradually to a cold (−10°) solution of 18 g. of stannous chloride dihydrate in 30 ml. of concentrated hydrochloric acid. The insoluble complex was removed, and stirred for 15 minutes with 22 ml. of 40% sodium hydroxide solution and sufficient crushed ice to keep the temperature below 10°. The cream-colored solid was filtered, suspended in ether, and shaken with 30 ml. of 5% sodium hydroxide solution until completely dissolved. The ether solution was washed, dried, and evaporated to a small volume, and petroleum ether was added to precipitate 4.1 g. of the crude, cream-colored hydrazine (m.p. 118–124°). Recrystallization from alco-

hol raised the melting point to 123–125°. The hydrazine gradually becomes tacky and appears to decompose in a few weeks.

Anal. Calc'd for $C_{18}H_{16}N_2$: C, 83.1; N, 6.2.

Found: C, 82.7; H, 6.4.

1-(4-o-Terphenylyl)-3-amino-5-pyrazolone (V) was obtained by the following procedure: A mixture of 1.5 g. of 4-hydrazino-*o*-terphenyl, 1.5 g. of ethyl β-ethoxy-β-iminopropionate, and 15 ml. of ethanol was heated to boiling, 0.5 ml. of acetic acid added, and the solution refluxed for two minutes; it became orange-red. It was cooled to room temperature, and freshly prepared sodium ethoxide solution (0.3 g. sodium in 10 ml. of absolute ethanol) added, after which the mixture was refluxed for one-half hour. It was then acidified (4 ml. of acetic acid), seeded with a previously prepared sample, and allowed to crystallize. After two hours, the pyrazolone was collected and recrystallized from 40 ml. of alcohol, with Darco. The recrystallized material, obtained in a yield of 24%, forms tan flakes, m.p. 223–225°.

Anal. Calc'd for $C_{21}H_{17}N_3O$: C, 77.1; H, 5.2; N, 12.9.

Found: C, 76.7; H, 5.1; N, 13.1.

1-(4-o-Terphenylyl)-3-benzamido-5-pyrazolone was made by benzoylating the above amine in dry pyridine, warming it on the steam-bath for one-half hour, followed by appropriate manipulation; the yield was 76%. It forms tan-colored crystals, m.p. 234–235°, after recrystallization from acetic acid.

4-(1'-Hydroxy-2'-naphthoylamido)-o-terphenyl (III) was prepared by heating a mixture of 5 g. of 4-amino-*o*-terphenyl and 7.3 g. of phenyl 1-hydroxy-2-naphthoate in a small distilling flask *in vacuo* at 140–160° for ten minutes. The molten liquid was then taken up in 300 ml. of alcohol, treated with Darco, and allowed to crystallize; the yield was 5.7 g. The pure amide melts at 181°.

Anal. Calc'd for $C_{29}H_{21}NO_2$: C, 83.9; H, 5.1; N, 3.4.

Found: C, 83.6; H, 5.1; N, 3.4.

4-Benzoylacetamido-o-terphenyl was obtained by gently heating a mixture of 2.5 g. of ethyl benzoylacetate, 10 ml. of xylene, and 2.5 g. of 4-amino-*o*-terphenyl for one hour, and allowing the alcohol formed to escape; the solution was cooled to 70°, and 4 volumes of technical hexane added. The product crystallized on chilling the solution; the yield was 2.6 g. (65%); m.p. 163–164°.

Anal. Calc'd for $C_{27}H_{21}NO_2$: C, 82.5; H, 5.3.

Found: C, 82.4; H, 5.7.

4-o-Methoxybenzoylacetamido-o-terphenyl was obtained similarly. It melts at 149–150°.

Anal. Calc'd for $C_{28}H_{23}NO_3$: C, 79.9; H, 5.5.

Found: C, 79.9; H, 5.6.

x-Benzoylacetamido-4-n-butyl-o-terphenyl was made in the same way, but failed to crystallize. It gave a yellow azomethine dye with oxidized 2-amino-5-diethylaminotoluene, as expected.

4,4''-Disalicylamido-o-terphenyl. A mixture of 2.0 g. of 4,4''-diamino-*o*-terphenyl, 3.3 g. of phenyl salicylate, and 25 ml. of α-methylnaphthalene was heated at 230° (bath temperature) for two hours. The resulting solution was cooled, and allowed to stand until crystallization was complete. The crystalline product was washed with ligroin, and recrystallized from 350 ml. of *p*-cymene. The light tan crystals weighed 2.2 g. and melted at 264–267°.

Anal. Calc'd for $C_{32}H_{24}N_2O_4$: C, 76.8; H, 4.8.

Found: C, 77.4; H, 5.2.

SUMMARY

The preparation and properties of a variety of amides, derived from 4-amino-*o*-terphenyls, are described. 4-Hydrazino-*o*-terphenyl and a pyrazolone containing the *o*-terphenyl group are included.

ROCHESTER 4, N. Y.

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[COMMUNICATION No. 1220 FROM THE KODAK RESEARCH LABORATORIES]

THE CHEMISTRY OF *o*-TERPHENYL. V. 4-VINYL-*o*-TERPHENYL

C. F. H. ALLEN, D. M. BURNESS, AND J. A. VANALLAN

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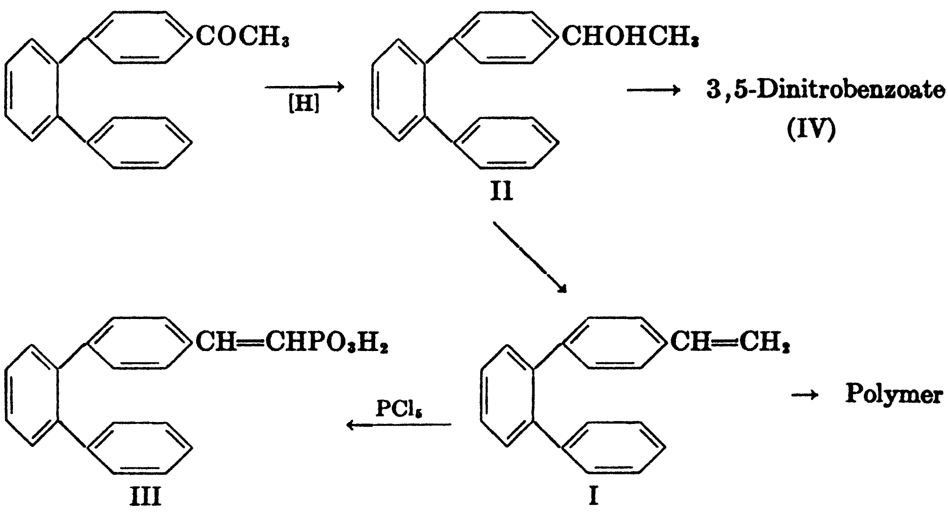
Since *o*-terphenyl can be acylated, in good yield, to form the 4-acetyl derivative (1, 1a) it seemed desirable to investigate the feasibility of converting this ketone to the substituted styrene, 4-vinyl-*o*-terphenyl (I). This hydrocarbon should be capable of undergoing polymerization to give a xenylated polystyrene.

4-Vinyl-*o*-terphenyl is readily obtained by the catalytic dehydration of methyl-4-*o*-terphenylylcarbinol (II) over aluminum oxide. As a styrene derivative, the new hydrocarbon decolorizes bromine instantly, and, when treated with phosphorus pentachloride in the usual way (2, 3, 4, 5), gives the phosphonic acid (III). It is readily polymerized by the action of peroxides and by heat, some of the hydrocarbon being lost during the preparation, for this reason.



The methyl-4-*o*-terphenylylcarbinol (II) was obtained by reduction of 4-acetyl-*o*-terphenyl in the presence of copper chromite. Since the carbinol is a liquid at room temperature, it was characterized by the formation of a solid 3,5-dinitrobenzoate (IV).

EXPERIMENTAL

Methyl-4-o-terphenylyl carbinol (II). A solution of 109 g. (0.4 mole) of 4-acetyl-*o*-terphenyl (1a) in 300 ml. of absolute alcohol and 1 g. of copper chromite catalyst were placed in a hydrogenation bomb of 1300-ml. capacity. Hydrogen was introduced to an initial pressure of 1100 p.s.i. (75 atm.), and the bomb heated, with shaking, to 150–160°. After one hour at this temperature, it was cooled, the contents were filtered, and the filtrate was evaporated under reduced pressure to a colorless syrup. Distillation *in vacuo* yielded 95

g. (86.5%) of the carbinol; b.p. 174°/1.5 mm. (187°/3.0 mm.); $n_D^{59.8}$ 1.6178. A portion was recrystallized from methanol by cooling in Dry Ice, but the crystals melted upon warming the sample to room temperature.

Anal. Calc'd for $C_{20}H_{18}O$: C, 87.6; H, 6.6.

Found: C, 87.6; H, 6.8.

The *3,5-dinitrobenzoate* (IV) was prepared by treating a solution of 0.9 g. of the carbinol in 3 ml. of pyridine with 0.88 g. of 3,5-dinitrobenzoyl chloride. The solution was warmed and poured into water. The insoluble residue was taken up in ether, and washed with dilute carbonate solution and water. The ether solution was evaporated, and the residue recrystallized twice from absolute ethanol, yielding pale yellow crystals, m.p. 147–147.5°.

Anal. Calc'd for $C_{27}H_{20}N_2O_6$: N, 6.0. Found: N, 5.8.

4-Vinyl-o-terphenyl (I). A solution of 70 g. of methyl-4-*o*-terphenylyl carbinol (II) and 80 ml. of xylene was dehydrated by Mowry's procedure (6) over aluminum oxide at 310–320°, under a pressure of 25 mm. Some polymeric material was noticed in the column and, later, in the distilling apparatus.

The styrene, b.p. 193–195°/4 mm., was obtained as a water-white liquid in a yield of 34 g. (52%). It is soluble in benzene, but insoluble in methanol. It decolorizes instantly a solution of bromine in carbon tetrachloride.

Anal. Calc'd for $C_{20}H_{16}$: C, 93.7; H, 6.3; mol. wt., 232.

Found: C, 93.5; H, 6.5; mol. wt., 216 (in boiling C_6H_6).

4-Vinyl-*o*-terphenyl slowly polymerizes on standing, in the absence of an inhibitor. With one-half per cent of benzoyl peroxide, it gives a tacky material which becomes brittle on cooling to 25°. This product is soluble in benzene but insoluble in acetone; its refractive index is 1.652.

(4-o-Xenyl)styrene-β-phosphonic acid (III). To a solution of 10.4 g. of phosphorus pentachloride in 25 ml. of dry benzene there was added 6.4 g. of 4-vinyl-*o*-terphenyl in 50 ml. of the same solvent. After standing overnight, the mixture was decomposed by pouring it into water, the benzene layer was separated, and the solvent removed. The residue was treated with a dilute alkaline solution prepared by mixing 10 ml. of 40% sodium hydroxide and 300 ml. of water, and decanted from considerable polymeric material. Upon acidification, an oily acid separated; the aqueous solution was decanted, and the acid recrystallized from boiling methanol, water being added to turbidity. The acid separated in shining plates, m.p. 209°, in a yield of 0.5 g. (4%).

Anal. Calc'd for $C_{20}H_{17}O_3P$: C, 71.4; H, 5.1.

Found: C, 70.9; H, 5.2.

SUMMARY

4-Vinyl-*o*-terphenyl and related substances have been prepared and described.

ROCHESTER 4, N. Y.

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[Communication No. 1221 from the Kodak Research Laboratories]

THE NITRATION OF TERPHENYLS

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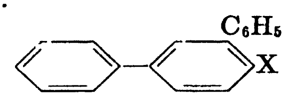
Received September 29, 1948

In connection with our investigation of the chemistry of *o*-terphenyl (1, 2, 3, 4, 5), the need arose for preparing monoamino derivatives of all the terphenyls. The most convenient procedure for their preparation appeared to be by reduction of the corresponding nitro compounds.

The usual method for securing nitro compounds, that is, employing a mixture of nitric and sulfuric acids, gives rise to polynitrated hydrocarbons. With *o*-terphenyl, for example, a mixture of unchanged hydrocarbon and polynitroterphenyls was obtained. The procedure in which ordinary fuming nitric acid (*d.* 1.49) in acetic acid is used, and which had been found satisfactory for the preparation of 4′-nitro-*m*-terphenyl (Ia) (6) failed to effect mononitration with *p*-terphenyl (7) and *o*-terphenyl. With *o*-terphenyl, when this procedure was used (with a 50% excess of nitric acid and the reaction heated for seventeen hours on a steam-bath), a large amount of *o*-terphenyl was recovered. The use of the stronger acid (*d.* 1.59) favored formation of dinitro derivatives.

This is not the only respect in which *m*-terphenyl differs from the other isomers. For example, *m*-terphenyl has been shown to undergo substitution invariably in the central ring (I) (6, 8, 9), whereas *o*- and *p*-terphenyl are attacked at the end carbon atom of an end ring.

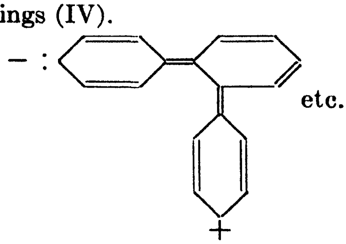


I

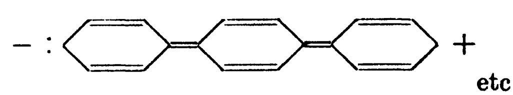
$X = NO_2$ (Ia)

$X = Br$ (Ib)

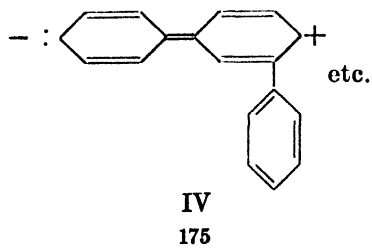
It is possible that these differences in the chemical behavior of *m*-terphenyl are due to its inability to form resonance structures which involve interaction of all three rings, as can *o*-terphenyl (II) and *p*-terphenyl (III). With *m*-terphenyl, no resonance structures can be written which simultaneously involve more than two rings (IV).



II



III



IV

However, this is probably only a partial explanation, for Pauling and Sherman (10) and Pullman (11) have indicated that the resonance structures which involve all three rings in the *ortho*- and *para*-terphenyls contribute to the complete structure of the molecules to a very small degree.

Eventually it was found that the desired mononitro-*o*-terphenyl could be obtained in the highest yield by carrying out the reaction in acetic acid and using a special mixture (2:1) of red, fuming (*d.* 1.59) and ordinary fuming (*d.* 1.49) nitric acids. The yields are still low, for there are always other products of nitration present, mostly isomeric mononitro compounds, which complicate the separation.

The procedure (2) previously described for preparing 4-nitro-*o*-terphenyl gave a mixture from which the desired isomer crystallized only after a year's standing, and the amine formed on reduction failed to remain crystalline. By the operations herein described a crystalline 4-nitro-*o*-terphenyl was obtained at once, and the amine is stable indefinitely.

Although 4-nitro-*p*-terphenyl had not hitherto been obtained by direct nitration (7), there was no difficulty in adapting the present procedure to *p*-terphenyl, and to 2,3,6-triphenyltoluene. Mononitro-4-butyl-*o*-terphenyl, similarly prepared, has been described in a previous paper (5).

In each instance, the nitro compounds were reduced to the corresponding amines. 4-*n*-Amylamino-*o*-terphenyl was obtained by direct alkylation of the amino compound.

EXPERIMENTAL

4-Nitro-o-terphenyl. A solution of 230 g. (1.0 mole) of Santowax O[1] in 500 ml. of glacial acetic acid was heated to 55–60°, and a solution of 50 ml. of fuming nitric acid (*d.* 1.49) and 100 ml. of red, fuming nitric acid (*d.* 1.59) was added dropwise during one hour. The temperature was kept at 55–60° by regulating the rate of addition and by cooling when necessary. The reaction mixture was then heated at the same temperature for five hours, cooled, and poured into 3000 ml. of water. It was allowed to stand overnight, whereupon the yellow tar became partially crystalline. The water was poured off, and the solid washed twice with water. Finally, the product was stirred with about 500 ml. of alcohol until it was completely crystalline and no lumps remained. It was filtered, washed with alcohol, and dried; the crude mixture of isomers weighed approximately 225 g. It was recrystallized from 2600 ml. of alcohol, with addition of sufficient 10% sodium carbonate solution to make the hot solution neutral to litmus.[2] Recrystallization from 1200 ml. of alcohol gave 104–110 g. (38–40%) of 4-nitro-*o*-terphenyl, melting at 111–114°.[3] This is satisfactory for most purposes. The pure substance, which melts at 115.5–116.5°, can be obtained by repeated recrystallization from acetic acid.

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[1] The Santowaxes are available commercially from the Monsanto Chemical Company. Santowax O contains approximately 95% *o*-terphenyl. Recrystallization of this material from ethanol before use, although raising its melting point 2 to 3°, did not improve the yield of the nitro compound.

[2] The solution was allowed to cool gradually to room temperature. Further cooling resulted in the separation of a mixture, containing a large amount of other isomers.

[3] Concentration of the filtrates gave only oils or low-melting solids which resisted purification. When the oil resulting from complete removal of the solvent was distilled *in vacuo*, a 30 to 40% yield of a mixture of mononitroterphenyls was obtained (b.p. 186–191°/2 mm.). Separation of this mixture is difficult and impractical.

Anal.[4] Calc'd for $C_{18}H_{13}NO_2$: C, 78.6; H, 4.7.
Found: C, 78.4; H, 4.5.

x-Nitro-o-terphenyl. Repeated recrystallization from ethanol and glacial acetic acid of the distillate obtained from the mother liquors in the preparation of 4-nitro-*o*-terphenyl (see footnote 3) yielded a small amount of an isomeric nitro-*o*-terphenyl. The compound crystallized from acetic acid as large, transparent, diamond-shaped crystals, m.p. 119.5°. The melting point of a mixture with 4-nitro-*o*-terphenyl was 88–102°.

Anal. Calc'd for $C_{18}H_{13}NO_2$: N, 5.1. Found: N, 5.1.

4-Amino-o-terphenyl. A hot solution of 140 g. of 4-nitro-*o*-terphenyl (m.p. 111–114°) in 1600 ml. of alcohol was placed in a low-pressure, copper bomb of 4500-ml. capicity. About 10 g. of Raney nickel and 5 g. of sodium carbonate were added, and hydrogen was introduced to a pressure of 50 lbs. The bomb was shaken and heated by steam until the absorption of hydrogen had ceased. It was necessary to introduce more hydrogen when the pressure dropped to 10–20 lbs. The hot reduction mixture was filtered by suction through a pad of Filter-Cel, the filtrate cooled to 0°, and the product removed by filtration. The first crop weighed 75.4 g., m.p. 117–118°. Concentration of the filtrate to 300 ml. gave an additional 41.8 g. (m.p. 116–117°), for a total yield of 117.2 g. (94%).

4-n-Amylamino-o-terphenyl. A mixture of 40 g. (0.163 mole) of 4-amino-*o*-terphenyl and 21.6 g. (0.204 mole) of *n*-amyl chloride was placed in a test tube (40 x 200 mm.) inside a 250-ml. bomb. Nitrogen was introduced to a pressure of 40 p.s.i. (2.7 atm.), and the bomb heated gradually, without shaking, to 180°. After one hour at 180–190°, the bomb was allowed to cool to room temperature. The product was removed, suspended in hot water, made alkaline with sodium carbonate, and extracted with ether. The ether solution was dried over potassium carbonate, and the ether evaporated. The residual oil was distilled *in vacuo*, yielding 22 g. (43%) of a nearly colorless, viscous oil with a strong blue fluorescence, b.p. 223–227° (4 mm.). Attempts to crystallize this oil were unsuccessful.

Anal. Calc'd for $C_{23}H_{25}N$: N, 4.4. Found: N, 4.6.

A *p-nitrobenzanilide* derivative was prepared by treatment of a dioxane solution of the amine and *p*-nitrobenzoyl chloride with 10% aqueous sodium hydroxide. The derivative separated as an oil which crystallized from alcohol after several days' standing Two recrystallizations from alcohol yielded yellow prisms, m.p. 95.5–97°.

Anal. Calc'd for $C_{30}H_{28}N_2O_3$: N, 6.0. Found: N, 6.1.

4-Nitro-p-terphenyl. To a suspension of 23 g. (0.1 mole) of Santowax P[1] in 70 ml. of glacial acetic acid, heated to 98°, was added, dropwise, a solution of 10 ml. of nitric acid (*d.* 1.59) and 5 ml. of nitric acid (*d.* 1.49). The temperature was held at 95–98° during the addition, and for one-half hour thereafter. The mixture was allowed to cool, and the acid liquors were decanted from the solid product. The latter was suspended in water, filtered, and washed with water, soda solution, and a little ether. The crude yield was 19.7 g. (72%), m.p. 205–210°. Recrystallization from nitroethane raised the melting point to 210–214°. The value given in the literature (7) for 4-nitro-*p*-terphenyl is 212–213°.

4-Amino-p-terphenyl. A suspension of 10 g. of crude 4-nitro-*p*-terphenyl in 220 ml. of absolute alcohol was reduced in a manner similar to that used for 4-amino-*o*-terphenyl. When the reduction was complete, an additional 200 ml. of alcohol was added to dissolve the product completely in the hot solvent. This solution was filtered and cooled to give 5.0 g. (56%) of 4-amino-*p*-terphenyl; m.p. 200–201°. The value given in the literature (7) for 4-amino-*p*-terphenyl is 197–198°.

4'-Nitro-m-terphenyl. When the conditions used for the nitration of *o*-terphenyl were applied to Santowax M[1] (*m-terphenyl*), the yield of 4'-nitro-*m*-terphenyl (b.p. 189–194°/1 mm.) was low (23%), and a large amount (55%) of *m*-terphenyl was recovered. Since satisfactory methods for the preparation of 4'-nitro-*m*-terphenyl have been published (6, 13), no further attempt was made to adapt the present procedure to the nitration of *m*-terphenyl.

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[4] This sample was prepared by Miss E. R. Webster, formerly of these Laboratories.

4'-Amino-m-terphenyl. This compound was prepared by hydrogenation of the nitro compound over Raney nickel, and purified through the hydrochloride (9). The yield of amine in the form of pure white needles, m.p. 67–68°, was 34%.

x-Nitro-2,3,6-triphenyltoluene. A suspension of 5.0 g. (0.0156 mole) of 2,3,6-triphenyltoluene (12)[6] in 25 ml. of glacial acetic acid was heated to 50°, and a solution of 1.5 ml. of nitric acid (*d.* 1.59), 0.75 ml. of nitric acid (*d.* 1.49), and 2 ml. of acetic acid was added in part. No reaction took place until the mixture was heated to 95–98°, at which temperature the remainder of the acid solution was added gradually. Complete solution soon took place, followed by the appearance of a white crystalline precipitate. Stirring was continued for one hour at 95–98°, and the mixture was then cooled, filtered, and washed with acetic acid. The yield was 3.8 g., m.p. 145–215°. After four recrystallizations from acetic acid, 1.1 g. (19%) of a pure nitro compound was obtained; m.p. 219.5–221.5°.

Anal. Calc'd for $C_{25}H_{19}NO_2$: N, 3.8. Found: N, 3.7.

x-Amino-2,3,6-triphenyltoluene. A suspension of 1.0 g. of this nitro compound in 100 ml. of absolute alcohol was reduced over Raney nickel. The yield of the amine in the form of pure white needles, m.p. 193–194°, was 0.75 g. (82%).

Anal. Calc'd for $C_{25}H_{21}N$: N, 4.2. Found: N, 4.1.

SUMMARY

Suitable conditions have been found for preparing mononitration products of several terphenyls. The corresponding amines and related compounds are also described.

ROCHESTER 4, N. Y.

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[6] We are indebted to Mr. J. A. VanAllan of these Laboratories for a supply of this compound.

[CONTRIBUTION FROM THE CHEMISTRY LABORATORIES OF THE UNIVERSITY OF TEXAS AND THE UNIVERSITY OF MICHIGAN]

AMINOPHENANTHRENE DERIVATIVES PREPARED BY THE SCHMIDT REACTION[1]

JOHN R. DICE[2] AND PETER A. S. SMITH[3]

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A method commonly used for the preparation of aminophenanthrenes and aminotetrahydrophenanthrenes has been the Beckmann rearrangement of the oximes of the acetyl- or benzoyl-phenanthrenes and hydrolysis of the resulting amides (1, 2). This paper reports the use of the Schmidt reaction (3) as an improved method for converting ketones to amides in this series.

The most satisfactory procedure (4) consisted of treating the ketone with an excess of sodium azide for several hours in trichloroacetic acid at about 60°. This method gave yields of the amides markedly better than those usually obtained in the Beckmann rearrangement; this is presumed to be due at least in part to milder reaction conditions, which result in only a small amount of decomposition.

Since the yields recorded for the Beckmann rearrangements are in terms of the free amines, the amides formed in this study were hydrolyzed to the corresponding amines in order to make the data comparable. The hydrolysis gave almost theoretical yields in every case. The yields are reported in Table II, together with the yields which have been reported for the corresponding Beckmann conversion.

From unsymmetrical ketones it is theoretically possible to get two isomeric amides by either the Beckmann or the Schmidt reactions. Investigations of the Beckmann conversion of aryl methyl ketones has shown that the N-arylacetamide is the predominant product, with the N-methylaroylamide rarely being formed in more than traces. The results of this investigation, added to the few cases already reported (3), suggest that the same generalization is valid for the Schmidt reaction. No attempt, however, was made to determine the trace amounts of N-methylaroylamides in our products. The diaryl ketone 1-benzoylphenanthrene has been shown by Bachmann and Boatner (2) to give 82% of 1-phenanthranilide and 18% of benz-1-phenanthrylamide on oximation and rearrangement. When this ketone was subjected to the Schmidt reaction in trichloracetic acid solvent with sulfuric acid as catalyst, nearly the same ratio of isomeric amides was obtained,[4] as determined by the same methods which Bachmann and Boatner used to examine the mixed amides obtained by the Beckmann rearrangement. Our experiment with 1-benzoylphenanthrene provides a gratify-

[1] That part of the work done at the University of Texas was supported by a grant from the University of Texas Research Institute (Project 186).

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[4] The results of a detailed investigation of the effect of structure on orientation in the Schmidt reaction by Smith and Horowitz will be reported elsewhere shortly.

ing demonstration of the role of acid strength in the formation of carbonium ions and the progress of the Schmidt reaction. A solution of 1-benzoylphenanthrene in trichloroacetic acid at 60° is yellow and does not react with hydrogen azide. The addition of an equivalent of sulfuric acid generated the intense blood-red color of the conjugate acid of 1-benzoylphenanthrene and immediately initiated a vigorous evolution of nitrogen. The more basic acetylphenanthrenes did not require the addition of sulfuric acid.

The suggestion of one of us (4) that the acid catalyst should not be stronger than necessary to carry out the Schmidt reaction at a convenient rate was checked by carrying out the reaction with various concentrations of sulfuric acid. 1-Acetonaphthone was treated with a standard amount of sulfuric acid of varying concentration (75% to 95%) and a fixed amount of sodium azide. The reaction products were hydrolyzed directly without purification in order to separate more easily the components, and the resulting 1-naphthylamine was isolated as the hydrochloride. The yields thus obtained are given in Table I. Analogous results were obtained from similar experiments on 2-acetonaphthone.

TABLE I

EFFECT ON YIELD OF VARIATION IN SULFURIC ACID STRENGTH

CONCENTRATION OF SULFURIC ACID	YIELD OF 1-NAPHTHYLAMINE HYDROCHLORIDE
75%	15%
85%	48%
90%	70%
95%	36%

Since any losses in the isolation procedure would be expected to be the same in all cases, the amount of final product should give an estimate of the efficiency of the original reaction. In general, the low yields with the more dilute acid were due to incomplete reaction, as shown by the large amounts of recovered ketone. The low yield with concentrated acid was due apparently to sulfonation, for the combined yields of recovered ketone and amine were far below 100%; no tetrazole formation was detected. Attempts to carry out Schmidt reactions in 95% sulfuric acid on 2- and 3-acetylphenanthrenes resulted in considerable nitrogen evolution, but the only result was incomplete recovery of impure starting material.

EXPERIMENTAL

1-Acetnaphthalide from 1-acetonaphthone. Effect of various concentrations of sulfuric acid. Since all the following reactions were run under as nearly identical conditions as possible, only the experiment with 90% sulfuric acid will be described. To an ice-cold mixture of 3.4 g. (0.02 mole) of 1-acetonaphthone and 20 ml. of 90% sulfuric acid was added 2.0 g. (0.03 mole) of powdered sodium azide (Eastman Kodak Co. Technical). Any lumps were broken up with a stirring rod and the mixture was kept at 0° to 5° with occasional stirring for eight hours. Nitrogen evolution was vigorous at the start of the reaction, but was inappreciable after six hours. The mixture was poured with stirring on ice and made basic with sodium

hydroxide. Evaporation of the benzene extracts gave a brown, pasty solid which was dissolved in a solution of 100 ml. of hot alcohol and 5 ml. of hydrochloric acid. After refluxing for twenty-four hours the solvent was evaporated, and the residue was made basic with 10% sodium hydroxide and extracted with benzene. The benzene layer was dried over sodium sulfate and treated with dry hydrogen chloride. The precipitated 1-naphthylamine hydro-

TABLE II

YIELDS AND PRODUCTS OF SOME SCHMIDT REACTIONS USING TRICHLOROACETIC ACID

SUBSTITUTED PHENANTHRENE	PRODUCT PHENANTHRENE	YIELD %	M. P. °C FOUND	M. P. °C REPORTED	YIELD BY BECKMANN CONVERSION %
7-Acetyl-9-methyl-1,2,3,4-tetrahydro- (5)	7-Amino-9-methyl-1,2,3,4-tetrahydro-	93	98–99	98.5–99.5 (1)	59 (1)
7-Acetyl-9-ethyl-1,2,3,4-tetrahydro-[a]	7-Acetamido-9-ethyl-1,2,3,4-tetrahydro-	99	188–190[b]		
9-Acetyl-2-methyl-1,2,3,4-tetrahydro- (6)	9-Amino-2-methyl-1,2,3,4-tetrahydro-	81	89–91	90–91	70 (6)
9-Acetyl-4-methyl-1,2,3,4-tetrahydro-	9-Amino-4-methyl-1,2,3,4-tetrahydro-	82	200–202 dec.	203–205 dec. (1)[c]	68 (1)
2-Acetyl-[a]	2-Amino-	88	82–84	85 (7)	79 (2)
3-Acetyl-[a]	3-Amino-	80	85–86	87.5 (7)	85 (2)
9-Acetyl- (2)	9-Amino-	73	135–137	137–138 (8)	48 (2)
1-Benzoyl-[a]	1-Benzamido- and 1-phenanthranilide	93–100	205–213		87 (2)

[a] Kindly supplied by Dr. W. E. Bachmann.

[b] A sample recrystallized for analysis melted at 193–194°: *Anal.* Calc'd for $C_{18}H_{21}NO$: C, 80.1; H, 7.86. Found: C, 80.2; H, 7.52. Analysis by Micro-Tech Laboratories, Skokie, Illinois.

[c] The picrate was used as a derivative, since the free amine is unstable.

chloride weighed 2.5 g. (70% over-all yield). A sample of 1-naphthylamine prepared from the hydrochloride melted at 48–50°.

Schmidt reaction using trichloroacetic acid as solvent. The following method was used with minor variations in all of the experiments. Yields and other pertinent data are given in Table II. In all cases the yield is calculated without correction for recovered starting material. To a solution of 0.02 mole of acetylphenanthrene or acetyltetrahydrophenan-

threne in 25 to 30 g. of trichloroacetic acid at 60° was added 2.0 g. (0.03 mole) of powdered sodium azide all at once. Any lumps were broken up with a stirring rod and the solution was maintained with occasional stirring at 60° for six to eight hours; in some cases a further small amount of sodium azide was added after three or four hours. The mixture was poured on 100 g. of ice. If the precipitated material was crystalline it was filtered, washed well with water, and dried. After one crystallization from alcohol it was usually pure enough for identification. If the reaction product was oily, it was extracted with benzene. The benzene layer was washed with 10% hydrochloric acid, 10% sodium hydroxide, and water. After being dried with sodium sulfate, the benzene was removed in a current of air and the residue was triturated with petroleum ether (60–70°) and if necessary, crystallized from alcohol. In several cases starting material could be recovered from the petroleum-ether wash. Hydrolysis of the amides was carried out following the method of Bachmann and Boatner (2) using alcoholic hydrochloric acid. The yield of the amines obtained by the hydrolysis of the amides varied from 96 to 100%. The over-all yields of the various amines are given in Table II.

Schmidt reaction on 1-benzoylphenanthrene. A solution of 1.0 g. of 1-benzoylphenanthrene in 15 g. of molten trichloroacetic acid was treated with 1.0 ml. of conc'd sulfuric acid and 0.3 g. of sodium azide at about 60°; two more portions of 0.1 g. each of sodium azide were added twenty minutes and thirty minutes from the start, respectively. One hour and thirty minutes from the start, the mixture was poured into *ca.* 100 ml. of cold water and the precipitated tan solid was collected and washed well with water; wt. in different runs 0.97–1.06 g. (93–100%), m.p. 205–213°. Part of the crude mixed amides was recrystallized twice from acetone, yielding 26% of nearly pure 1-phenanthranilide, m.p. 245–247°. This is essentially the same as the experience of Bachmann and Boatner (2) with the mixed amides from the Beckmann rearrangement. Another portion (0.32 g.) was refluxed with alcoholic hydrochloric acid for 19 days; there was obtained 0.03 g. (15%) of 1-phenanthrylamine, m.p. 143–145°, and 0.23 g. (72%) of 1-phenanthranilide, m.p. 249–250° after decolorizing with charcoal in acetone. Bachmann and Boatner, working on a much larger scale but with otherwise similar conditions, obtained 18% of 1-phenanthrylamine and 82% of 1-phenanthranilide of unspecified purity.

Hydrolysis of 0.97 g. of crude mixed amides with 25 ml. of glacial acetic acid and 5 ml. of conc'd hydrochloric acid in a sealed tube at 160–220° for 10 hrs. yielded 0.15 g. (23%) of crude 1-phenanthrylamine, identified by conversion to its picrate, m.p. 203–204° in 95% yield; 0.32 g. (44%) of 1-phenanthroic acid, m.p. 228–232°, and some impure neutral material presumed to be unhydrolyzed 1-phenanthranilide. Bachmann and Boatner report 1-phenanthrylamine picrate to melt at 203–204°, and 1-acetamidophenanthrene to melt at 218.5–219.5°. We obtained the m.p. 203–204° for the picrate of the reaction product as ordinarily collected. However, if a small first crop (m.p. 203–204°) was taken, and the remainder collected as a large second crop; the m.p. was 215–216°. Both crops of picrate gave 1-acetamidophenanthrene, m.p. 223.5–224.5° separately and when mixed with each other, in high yield; and when samples of picrate from each melting range were mixed an intermediate m.p. was obtained. All these results were reproducible. Bachmann and Boatner obtained 14% of 1-phenanthrylamine and 63% of 1-phenanthroic acid from a similar hydrolysis of the mixed amides from the Beckmann rearrangement.

SUMMARY

The use of the Schmidt reaction as a superior method for the preparation of naphthyl- and phenanthryl-amines is described. In this series of compounds this method gives better yields and is simpler to carry out than the usual Beckmann rearrangement. A study was made of the effect of certain experimental conditions on the yield of the reaction.

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[CONTRIBUTION No. 167 FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, FORDHAM UNIVERSITY]

STUDIES IN THE THIOPHENE SERIES. II.[1] PREPARATION AND PHYTOCHEMICAL REDUCTION OF 2,2′-THENOIN AND 2,2′-THENIL

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Received October 19, 1948

In continuation of investigations in the thiophene series (1), conducted in our laboratories, it was deemed suitable to study some typical aromatic aldehyde reactions as applied to the thiophene aldehydes. The benzoin condensation leading to the formation of hydroxy ketones had not been successfully attempted with thiophene-2-aldehyde.[3] It has been previously reported that the application of potassium cyanide to thiophene-2-aldehyde causes complete resinification of the thiophene ring (2). While it is true that a water-alcohol solution of the aldehyde in the presence of cyanide ion does yield a somewhat tarry product, suitable recrystallization methods can be applied to obtain the hydroxy-ketone, 2,2′-thenoin (I).

This compound gives a color reaction similar to that shown by benzoin and other acyloin condensation products in the presence of alcoholic alkali. Benzoin gives a reddish purple color, furoin a deep blue-green color and, with thenoin a deep green coloration is produced, which disappears upon shaking and reappears when the solution is allowed to stand. The hydroxy ketone may be oxidized by iodine in the presence of sodium methoxide (3) to give the diketone, 2,2′-thenil (II), in excellent yields. The color reaction is not given by this compound. The quinoxaline derivative of 2,2′-thenil (IV) was prepared to verify the presence of an *alpha-diketo* grouping.

It has been shown previously (4) that carbonyl groups can be phytochemically reduced and this procedure has been applied to aromatic and heterocyclic hydroxyketo and diketo compounds, such as benzoin, benzil, furoin, and furil. Thiophene-2-aldehyde has also been reduced by the action of fermenting yeast to thiophene-2-carbinol (5). It was considered of interest, therefore, to attempt the phytochemical reduction of 2,2′-thenoin and 2,2′-thenil to determine the effect of the thiophene ring as compared to the benzene and furan rings. Since 2,2′-thenoin gives the above mentioned color reaction even in great dilutions and when added to a yeast suspension, its presence can be easily detected. The course of reactions taking place may be visualized in Chart I.

In the first attempt to reduce 2,2′-thenoin it was found that an *oxidation* had taken place to yield 2,2′-thenil instead of the expected 2,2′-dihydrothenoin (III). Although it is known that hydroxyketo compounds of this type are sus-

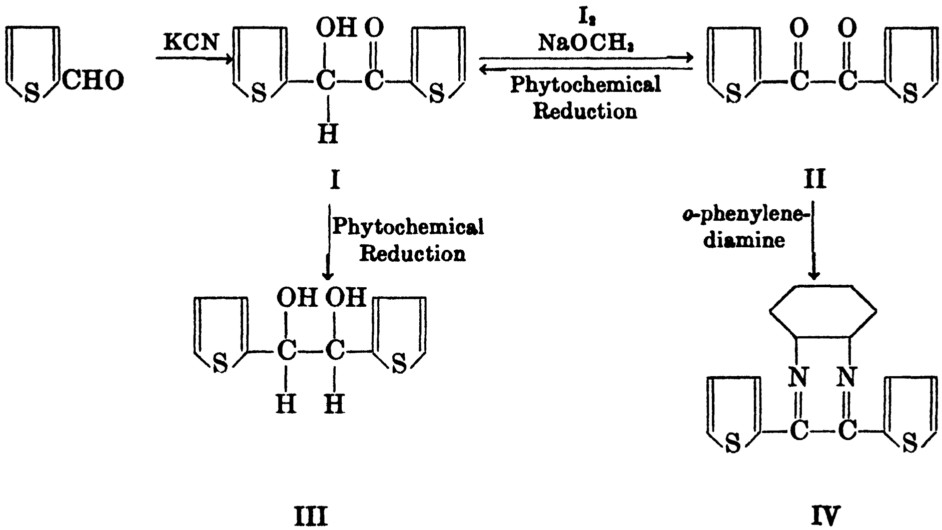
[1] For the first paper in this series see Ref. (1). This investigation was carried out with the aid of a grant from the Office of Naval Research.

[2] Fellow of the Department of Industrial Research, Banco de Mexico, S. A. Mexico City, Mexico.

[3] For 3-substituted thiophenes see Ref. (6).

ceptible to oxidation by air in alkaline solution, it did not seem likely that the oxidation resulted in this manner, since the fermentation mixture is acidic. Furthermore, in a separate experiment, in which air was vigorously bubbled through a slightly acidic alcoholic solution of 2,2′-thenoin, 2,2′-thenil was not obtained. It appears, therefore, more probable that the dehydrogenating enzyme system present in the yeast had effected the conversion. Since this attempt had been run with vigorous stirring to speed up the reaction, and air was not excluded from the flask, the conversion was carried on without stirring and in a carbon dioxide atmosphere. In this case it was found that thenoin could be reduced to dihydrothenoin and that thenil was first converted to thenoin and

CHART I



then to the dihydroxy compound. It is interesting to note that thenoin differs significantly from benzoin, since reduction products were not obtained from the latter by phytochemical means (4). Furthermore, unlike furil, in which reduction products are present almost immediately, it was not until the third day that the fermentation mixture containing 2,2′-thenil gave a color reaction for 2,2′-thenoin.

EXPERIMENTAL[4]

2,2′-Thenoin (I). In a 500-cc. flask fitted with a reflux condenser were placed 33.6 g. (0.3 mole) of thiophene-2-aldehyde (1), 100 cc. of ethyl alcohol, and 40 cc. of water. The solution was placed on a steam-bath and brought to reflux. A solution of 4 g. of potassium cyanide in 20 cc. of water was added, resulting almost immediately in a deep green coloration. After refluxing for two hours, the solution was cooled, acidified with acetic acid and allowed to stand for two days in an ice-box with occasional shaking. The somewhat tarry precipitate was filtered and washed successively with small portions of cold alcohol and

[4] The analyses presented were carried out by M. Bier of this laboratory.

water. Recrystallization from methyl alcohol with charcoal yielded 10.2 g. (30%) of light cream colored crystals of 2,2′-thenoin. Upon microsublimation *in vacuo* we obtained white crystals, m.p. 108–109°.

Anal. Calc'd for $C_{10}H_8O_2S_2$: C, 53.55; H, 3.59.

Found: C, 53.85; H, 3.53.

2,2′-Thenil (II). Thenoin (4.2 g., 0.02 mole) was dissolved in 90 cc. of pure methanol and to the boiling solution was added a freshly prepared hot solution of sodium methoxide, prepared by dissolving 1 g. of sodium in 20 cc. of pure methanol. To the boiling solution was added in small portions 5.6 g. of iodine. Upon cooling there was obtained 3.7 g. of bright yellow crystals. Recrystallization from alcohol with charcoal yielded 3.3 g. (79%) of 2,2′-thenil, m.p. 81–82°.

Anal. Calc'd for $C_{10}H_6O_2S_2$: C, 54.04; H, 2.72.

Found: C, 54.00; H, 2.71.

It is necessary to use pure methanol, since small amounts of contaminants, such as ethyl alcohol or acetone, may yield iodoform.

2,3-bis-(2-Thienyl)quinoxaline (IV). Formed by refluxing 1 g. of 2,2′-thenil with 0.8 g. of *o*-phenylenediamine dihydrochloride in 30 cc. of ethanol. Recrystallization gave white crystals m.p. 143–144°.

Anal. Calc'd for $C_{16}H_{10}N_2S_2$: C, 65.27; H, 3.43.

Found: C, 65.35; H, 3.56.

Phytochemical reduction of 2,2′-thenoin. To 500 cc. of a 10% sucrose solution in a 3-liter flask, 50 g. of baker's yeast[5] was added. After the onset of the fermentation, 3.1 g. of 2,2′-thenoin in 40 cc. of ethyl alcohol (95%) was added drop by drop at room temperature, a carbon dioxide source was connected to the flask and the mixture was saturated with carbon dioxide before and during the reaction. After 12 hours, samples were taken from the flask and it was found that only a slight Fehling test was given, but a strong color indicated the presence of unchanged thenoin. Accordingly, 250 cc. of the sugar solution and 25 g. of yeast were added to the flask. This procedure was continued each day for a total of five days. On the fourth day, the reaction for thenoin was negative. After the fifth day, the fermentation mixture was evaporated to one-third of its volume on a steam-bath and the syrupy liquid treated with sodium carbonate until alkaline, and then saturated with sodium sulfate. The material was extracted exhaustively with ether and the ethereal solution filtered through a sintered glass funnel and evaporated under reduced pressure. The residual oil was dissolved in alcohol and enough water added to cause cloudiness. After standing in the ice-box for two weeks, the oil crystallized. Filtration and recrystallization from benzene and petroleum ether with charcoal yielded 1.3 g. of dihydrothenoin, white crystals m.p. 90–91°. The compound showed slight optical activity, $[\alpha]_D^{25}$ = +0.95° (α = +0.02, c = 2.09997, l = 1; alcoholic solution).

Anal. Calc'd for $C_{10}H_{10}O_2S_2$: C, 53.08; H, 4.41.

Found: C, 53.05; H, 4.33.

Dibenzoate. Crude dihydrothenoin (1 g.) was dissolved in 6 cc. of anhydrous pyridine to which 2.0 g. of benzoyl chloride was added. The mixture was heated over a low flame for several minutes, and after cooling, 35 cc. of water was added, resulting in a yellow oil. The supernatant liquid was decanted and the oil washed with several portions of water. The substance was then dissolved in hot alcohol, cooled, and allowed to crystallize. The resulting substance was recrystallized from alcohol with charcoal to yield white crystals. m.p. 186–186.5°.

Anal. Calc'd for $C_{24}H_{18}S_2O_2$: C, 66.34; H, 4.17.

Found: C, 66.40; H, 4.25.

Phytochemical reduction of 2,2′-thenil. The same procedure as outlined above was followed, except that 6 g. of thenil was added to the fermentation mixture. The test for

[5] The yeast used in these experiments was obtained through the courtesy of Mr. G. W. Kirby of the Fleischmann Laboratories, New York, N. Y.

thenoin was negative until the third day, indicating that the progress of the reaction was slow. At the end of the fifth day the fermentation mixture was concentrated, extracted with chloroform, and the chloroform extract filtered and evaporated *in vacuo*. The resulting yellow oil was dissolved in hot alcohol, and water added to cloudiness. After several days in the ice-box, the solid material was filtered. Since thenil is less soluble in alcohol than thenoin, the crude material was treated with alcohol, until the residue did not give a test for thenoin. This residue (1.5 g.) proved to be mainly unchanged thenil m.p. 79–81°. A mixed melting point showed no depression. The alcoholic solution was evaporated and the residue recrystallized from a water-alcohol mixture. There was obtained 0.4 g. of 2,2′-thenoin, which after sublimation *in vacuo* had m.p. 107–108°. A mixed melting point showed no depression. The fermentation mixture, which had been extracted with chloroform, was then extracted with ether, and the procedure indicated for the isolation of dihydrothenoin was followed. There was obtained 0.3 g. of dihydrothenoin, m.p. 90–91°. The color reaction for 2,2′-thenoin was carried out by mixing 1 cc. of the fermentation mixture with 3 cc. of alcohol and then adding a drop of concentrated alkali. If 2,2′-thenoin is present, a green color soon appears, which disappears upon shaking and reappears upon standing.

SUMMARY

1. A method is presented for the preparation of 2,2′-thenoin and 2,2′-thenil.

2. Phytochemical reduction was shown to be applicable to both compounds.

3. Differences in the phytochemical reducibility of these compounds in contrast to benzoin and furil were observed.

New York 58, N. Y.

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NEW REACTIONS AND DERIVATIVES OF UREA. SYNTHESIS OF TRIAZINES[1]

ALFRED MAX PAQUIN

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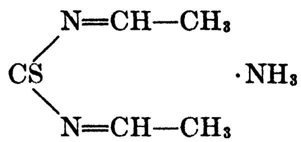
Investigations dealing with the reaction of urea with alcohols (1), with ketones and formaldehyde (2), with diamines, alkylene oxides and certain unsaturated compounds (3) have been described elsewhere. Likewise the formation of new complex compounds of urea with metals, ammonia, and amines has been reported (2). In the present communication the results of a study of the reaction of urea and related compounds on aldehyde-ammonia and aldehyde-amine derivatives is presented.

Nencki (4) described the formation of a crystalline substance to which he assigned the structure of an ammoniated complex of diethylidenethiourea (I) from the reaction of one mole of thiourea with two moles of acetaldehyde-ammonia.

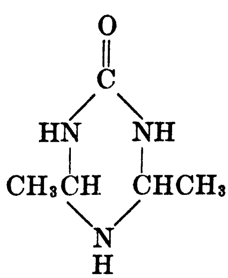


I

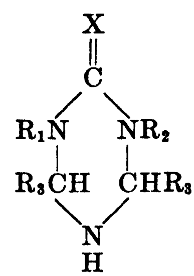
Dixon (5) confirmed the formation of Nencki's compound, but was unable to prepare the analogous compound from urea.

It has now been found that, under proper conditions, urea does indeed react with acetaldehyde-ammonia, and that the nature of the product is dependent on the conditions of the experiment. When moist acetaldehyde-ammonia is intimately mixed with dry urea, immediate liquefaction accompanied with a slight evolution of heat occurs. Extraction of the cooled melt with ether gave a substance assigned the structure of N,N′-bis-(1-aminoethyl)urea (II)

II



III



IV

[1] The work reported in this paper was done in the laboratories of the I. G. Farbenindustrie at Hoechst-am-Main, Germany. Due to the author's political exclusion from the laboratories in the summer of 1944, the investigations could not be completed, and certain details are no longer available.

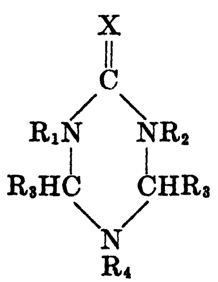
on the basis of elementary analysis. II readily lost ammonia, even at the boiling point of ether, to yield the triazine III, with the result that preparations of II were always somewhat contaminated by III. By carrying out the reaction in water or alcohol at 40–50°, satisfactory yields of III can be obtained directly. The triazine is a weak base. It forms salts with strong acids, a characteristic difficultly soluble picrate, and a well crystallizing double salt with silver nitrate. Aqueous solutions of the triazine decompose slowly on boiling, particularly when slightly acidified, with the formation of ammonia, acetaldehyde, and urea. Analogous triazines of the general type of IV have been prepared by reaction of thiourea, guanidine, and N,N′-disubstituted ureas with ammonia compounds of various aldehydes. The triazines in general melt above 150° when pure. However when moist or impure they undergo decomposition at temperatures of about 100°, with elimination of ammonia and formation of resins.

It is not necessary to prepare the aldehyde-ammonia derivatives separately, as under the proper conditions the triazines may be obtained directly from the urea compound, ammonia, and aldehyde.

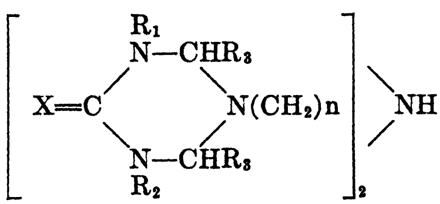
Formaldehyde forms an exception to the above general reactions. Hexamethylenetetramine was the only product formed when urea is used in the reaction. With thiourea the product was the double salt of two moles of thiourea and one mole of hexamethylenetetramine.

By substituting aliphatic amines for ammonia in the reaction, triazines of the type of V result. In this reaction, the use of formaldehyde leads to a triazine.

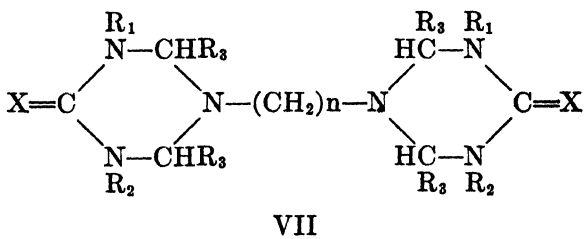
The triazines prepared from diamines on heating lose ammonia to yield bis-triazines of the type of VI.



V



VI



VII

By the reaction of one mole of diamine with two moles of urea compound and four moles of aldehyde, bis-triazines of type VII may be prepared.

TABLE I

SUBSTITUTED HEXAHYDROTRIAZINES (FORMULA V). $R_1 = R_2 = R_3 = H$

X	R_4	YIELD %	M.P. °C.	SOLVENT FOR CRYST.	CALC'D					FOUND				
					% C	% H	% N	% S	M.W.	% C	% H	% N	% S	M.W.[2]
O	CH_3	68	199 d.	ethanol	41.0	7.7	35.9		115	40.6	7.6	35.8		108, 117, 124
O	n-C_3H_7	62	182	ethanol	50.3	9.1	29.4		143	50.7	9.3	29.7		148, 154, 159
O	iso-C_4H_9	51	194	ethanol[a]	53.5	9.5	26.8		157	53.2	9.4	27.2		134, 141, 154
O	C_6H_{11}	64	205 d.	ethanol[a]	59.1	9.3	22.9		183	59.2	9.4	22.6		186, 191, 196
S	CH_3	63	169 d.	ethanol-benzene (1:1)	36.6	6.9	32.0	24.4	131	36.6	7.0	32.0	24.3	126, 129, 136
S	iso-C_4H_9	68	142	ethanol	48.6	8.7	24.3	18.5	173	48.7	8.6	24.1	18.3	152, 161, 170
S	C_6H_{11}	72	176	ethanol	54.2	8.5	21.0	16.1	199	54.0	8.6	20.9	15.9	192, 197, 202
O	$CH_2CH_2NH_2$	68	176–7	25% ethanol[a]	41.7	8.3	38.8		144	41.5	8.4	38.7		139, 146, 151
S	$CH_2CH_2NH_2$	54–88	140 d.	water	37.3	7.5	35.0	20.0	160	37.0	7.6	35.3	19.8	151, 158, 164
O	CH_2CH_2OH			Non-cryst.										

[a] It was necessary to heat to 135° to secure crystallization.

EXPERIMENTAL

4-Keto-2,6-dimethylhexahydro-1,3,5-triazine. V. $X = O$, $R_1 = R_2 = R_4 = H$, $R_3 = CH_3$. A mixture of 60 g. of urea, 149 g. of freshly prepared acetaldehyde-ammonia (containing 18% of water) and 30 g. of water was heated with stirring at 55–60° until a clear liquid resulted. The temperature was then raised to 75° during half an hour. Evolution of ammonia occurred and the product began to crystallize from the melt. After cooling to 0° the semi-solid crystalline mass was filtered and recrystallized from alcohol-acetone (4:1) yielding 71% of the triazine which melted at 190° (dec.).

Anal. Calc'd for $C_5H_{11}N_3O$: C, 46.5; H, 8.5; N, 32.5; M.W., 129.

Found: C, 46.5; H, 8.6; N, 32.5; M.W.,[2] 123, 127, 132.

The substance is soluble in cold water and ethanol. It forms an insoluble phosphate and picrate and a well-crystallizing double salt with silver nitrate.

The same substance may be prepared alternatively as follows. To 136 g. of 25% aqueous ammonia cooled to 5° was added slowly through a dropping-funnel extending to the bottom of the flask 88 g. of acetaldehyde cooled to 0°. The mixture was stirred and cooled so that the temperature did not exceed 15°. After half an hour a solution of 60 g. of urea in 60 g. of water was added and the mixture was heated gradually to 70–75°. The triazine was isolated as above.

4-Thio-2,6-dimethylhexahydro-1,3,5-triazine. V. $X = S$, $R_1 = R_2 = R_4 = H$, $R_3 = CH_3$. This was prepared as above, from 76 g. of thiourea, and 149 g. of 82% acetaldehyde-ammonia in 420 g. of water at 65–70° for twenty minutes. The yield of material melting at 180° (dec.) after recrystallization from water was 87%. The substance is slightly soluble in cold water and alcohol.

Anal. Calc'd for $C_5H_{11}N_3S$: C, 41.4; H, 7.6; N, 28.9; S, 22.0; M.W., 145.

Found: C, 41.4; H, 7.6; N, 28.8; S, 21.9; M.W.,[2] 142, 148, 153.

4-Imino-2,6-dimethylhexahydro-1,3,5-triazine. V. $X = NH$, $R_1 = R_2 = R_4 = H$, $R_3 = CH_3$. This was prepared from 122 g. of guanidine nitrate, 149 g. of 82% acetaldehyde-ammonia in 70 g. of water at 70–75° for twenty-five minutes. The yield of material melting at 156–157° (dec.) after recrystallization from aqueous ethanol was 54%.

Anal. Calc'd for $C_5H_{12}N_4$: C, 46.8; H, 9.4; N, 43.7; M.W., 128.

Found: C, 46.8; H, 9.5; N, 43.7; M.W.,[2] 124, 128, 133.

4-Keto-2,3,5,6-tetramethylhexahydro-1,3,5-triazine. V. $X = O$, $R_1 = R_2 = R_3 = CH_3$, $R_4 = H$. This was prepared as above from 88 g. of N,N′-dimethylurea, 149 g. of 82% acetaldehyde-ammonia, and 80 g. of water at 70–75° for thirty minutes. The yield was 55%.

Anal. Calc'd for $C_7H_{15}N_3O$: C, 53.4; H, 9.6; N, 26.6; M.W., 157.

Found: C, 53.5; H, 9.6; N, 26.8; M.W.,[2] 142, 148, 154.

4-Keto-2,6-di-n-propylhexahydro-1,3,5-triazine. V. $X = O$, $R_1 = R_2 = R_4 = H$, $R_3 = C_3H_7$. This was prepared as above from 60 g. of urea, 212 g. of 84% butyraldehyde-ammonia and 50 g. of water at 70–75° for twenty-five minutes. The yield of material recrystallized from alcohol was 74%.

Anal. Calc'd for $C_9H_{19}N_3O$: C, 58.4; H, 10.3; N, 22.7; M.W., 185.

Found: C, 58.3; H, 10.3; N, 22.6; M.W.,[2] 174, 182, 191.

4-Keto-2,6-dibenzylhexahydro-1,3,5-triazine. V. $R_1 = R_2 = R_4 = H$, $R_3 = CH_2C_6H_5$. This was prepared in 68% yield from 60 g. of urea, 299 g. of 91% phenylacetaldehyde-ammonia in a mixture of 70 g. of water and 160 g. of ethanol at 70–75° for thirty-five minutes. It was recrystallized from ethanol.

Anal. Calc'd for $C_{17}H_{19}N_3O$: C, 72.6; H, 6.8; N, 14.9; M.W., 281.

Found: C, 72.5; H, 6.9; N, 14.8; M.W.,[2] 286, 289, 294.

N,N′-bis-(1-aminoethyl)urea. II. A mixture of 60 g. of urea and 149 g. of freshly prepared acetaldehyde-ammonia containing 18% of water was ground in a mortar. Liquefaction occurred and the temperature of the mixture rose to about 37°. After ten minutes

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[2] Ebullioscopic in ethanol.

the mixture was cooled to 20° and shaken with ether several times. After drying and removal of the ether at the water-pump, a substance melting at 41–46° was obtained. The material apparently was contaminated with the triazine III, since repeated analysis at best approximated the values demanded for the urea II.

4-Keto-1-methylhexahydro-1,3,5-triazine. V. $X = O, R_1 = R_2 = R_3 = H, R_4 = CH_3$. To a solution of 60 g. of urea in 125 g. of 25% aqueous methylamine was added 150 g. of 40% formaldehyde solution at 10–15° with stirring and cooling. After stirring with cooling for an additional hour, the mixture was heated to 55° during half an hour. After distillation of the water at reduced pressure, the crystalline residue was recrystallized from ethanol. Analytical data for this and similar compounds prepared by the same general procedure are given in Table I.

β,β′-Bis-(4-keto-1,3,5-hexahydro-1-triazinyl)ethylamine. VI. $X = O, R_1 = R_2 = R_3 = H, n = 2$. When 4-keto-1-aminoethylhexahydro-1,3,5-triazine was heated to its melting point, loss of ammonia occurred. This process was completed by heating at 155–160° until evolution of ammonia ceased. Analyses proved the structure of the compound, but these are not at hand.[1] A similar reaction took place when the analogous sulfur compound was heated.

1,2-Bis-(4′-thio-1,3,5-hexahydro-1-triazinyl)ethane. VII. $X = S, R_1 = R_2 = R_3 = H, n = 2$. To a solution of 76 g. of thiourea in 200 g. of water, 40 g. of 76% ethylenediamine and 200 g. of 30% formaldehyde were added simultaneously through two dropping-funnels at 20–25°. The mixture was stirred and cooled. A white powder which changed gradually into an opaque soft resinous mass separated. This crystallized after a short time. Recrystallization from ethanol gave 75% of material melting at 209–210° (dec.).

Anal. Calc'd for $C_8H_{16}N_6S_2$: C, 36.6; H, 6.8; N, 32.0; S, 24.4; M.W., 260.

Found: C, 37.0; H, 6.7; N, 32.3; S, 24.7; M.W.,[2] 248, 256, 263.

The analogous oxo-compound may be similarly prepared from urea.

SUMMARY

Aldehydes forming stable ammonia addition compounds react with urea and its derivatives to form 1,3,5-triazines having an NH group at the 1-position. The same reaction may be realized with urea derivatives, aldehydes and ammonia. Intermediates in these reactions are N,N′-bis-(amino-alkyl or -aryl) ureas.

1,3,5-Triazines with an alkyl or aryl substituted 1-imino group may be prepared from the corresponding amines and aldehydes, including formaldehyde. Amines with a hydroxyl group give rise to triazines containing a reactive hydroxyl, suited to further substitutions.

Reaction of diamines with one mole of urea compound gives triazines with a free amino group, which may condense to a bis-compound with loss of ammonia.

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[Contribution from the Research Laboratory of Endo Products Inc.]

THE ISOMERIZATION OF MORPHINE TO O-DESMETHYLTHEBAINONE[1]

ULRICH WEISS and NATHAN WEINER

Received June 11, 1948

The isomerization of morphine (I) to dihydromorphinone (II) (in acidic medium) in the presence of noble metal catalysts is well known (1). We have observed that in the course of this interconversion (1a) there is also produced a smaller amount of a hitherto unrecorded isomer of morphine. Under appropriate conditions we have been able to achieve about 60% conversion of morphin toe this new isomer. Separation of the new compound from the accompanying dihydromorphinone is effected through their different solubilities in chlorofo-Im or pyridine. The work to be presented indicates almost unequivocally that the compound has the structure III. It could best be designated as O-desmethylthebainone.

The new compound is a homogeneous, well defined chemical individual, as demonstrated by the uniformity of the free base obtained from various fractions of the recrystallized hydrochloride. The analytical values agree well with those for the composition $C_{17}H_{19}NO_3$. With acetic anhydride it forms an easily saponified diacetate, indicating two actual or potential hydroxyl groups. Molecular weight determination on this compound cryoscopically in benzene or camphor (Rast) gave values corresponding to a diacetate of $C_{17}H_{19}NO_3$, whereas the parent compound III was too insoluble in the usual solvents for cryoscopic or ebullioscopic molecular weight measurements. Absorption of one mole of hydrogen in the presence of palladium to give compound IV with persistence of the original carbonyl group (formation of oximes and thiosemicarbazones of both compounds) demonstrates the presence of the double bond.

Evidence for placing the ethylenic double bond in the 7,8-position, in conjugation with the carbonyl group, was obtained in several different ways. With aqueous alkali, in the presence of sodium hydrosulfite, III produces a light yellow color. It has been shown (2) that, among ketonic morphine derivatives, this color reaction is given only by thebainone, 14-hydroxythebainone, and sinomenine, all α,β-unsaturated ketones.[2] Schöpf has considered this as a characteristic group reaction. Some small doubt may be cast upon this generalization by our observation that the dihydro derivative (IV), under the same conditions provides a solution which stays colorless for only a short time, rapidly becoming brown in spite of the presence of hydrosulfite. However, this color is easily distinguished from the yellow producd by III.

Speyer *et al.* (3) have observed that oximes of α,β-unsaturated ketones undergo catalytic hydrogenation and hydrogenolysis simultaneously to ammonia and the

[1] Presented before the Organic Division, 114th meeting of the American Chemical Society, St. Louis, Mo., Sept. 7, 1948.

[2] With those compounds which are less sensitive to oxygen than III or IV, no hydrosulfite was used.

saturated ketone. In conformity, the oxime of III upon catalytic hydrogenation gave ammonia and IV, isolated as the oxime hydrochloride.

It was hoped that a study of the ultraviolet absorption spectra of III and IV, and comparison with the spectra of other possibly related morphine derivatives

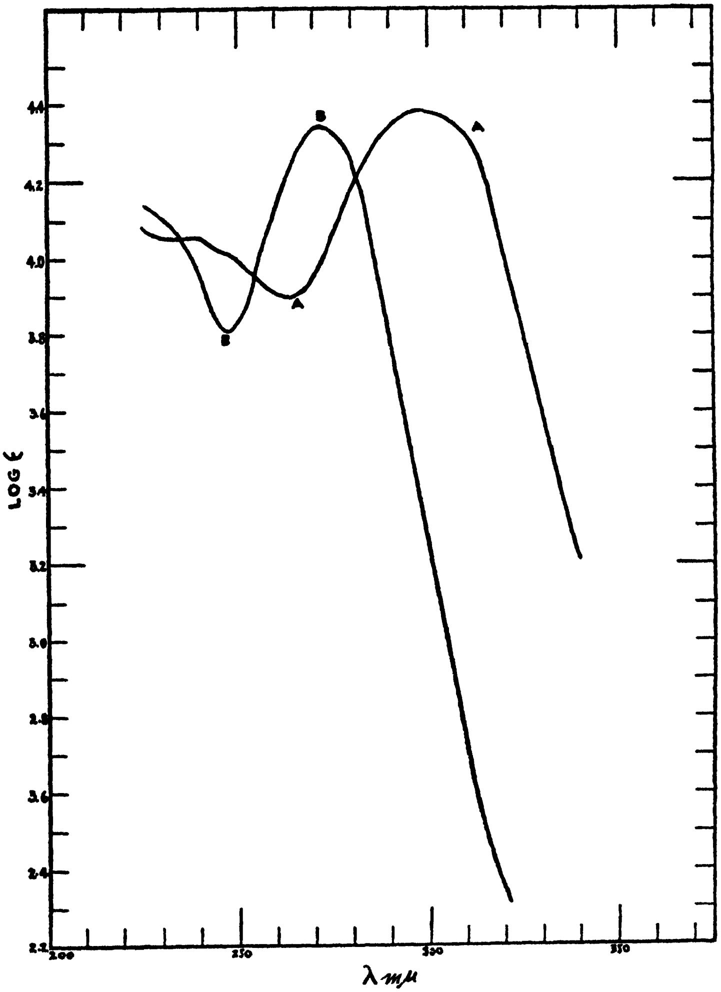


FIG. 1. ULTRAVIOLET ABSORPTION SPECTRA IN METHANOL OF THE THIOSEMICARBAZONE HYDROCHLORIDES OF O-DESMETHYLTHEBAINONE (III), (CURVE A) AND OF O-DESMETHYLDIHYDROTHEBAINONE (IV), (CURVE B)

would give supporting evidence for the conjugated system. Unfortunately, the significant band for such a conjugated system (225 ± 5 mμ) (4) was completely obscured by the end absorption exhibited by all morphine derivatives. Examination of the absorption spectrum of the thiosemicarbazones[3] of III and IV gave

[3] We are indebted to Dr. R. B. Woodward of Harvard University for this suggestion and for the reference to the work of Gillam.

final and conclusive proof of the presence of the conjugated system. Evans and Gillam (5) found that thiosemicarbazones of unsaturated ketones are characterized by a very high absorption maximum at 301.5 ± 2 mμ (ϵ = 20,000–30,000) and a lesser one at 245 ± 4 mμ (ϵ = 7,000–13,000).

The semicarbazones of saturated ketones and of unsaturated ketones other than α,β, have maxima at 270 and 230 mμ. The thiosemicarbazone hydrochlorides of III and IV fit very well into this pattern (see Fig. 1).

Indications that compound III resulted by opening of the oxygen bridge were first obtained from color reactions. Morphine, and many of its derivatives, in which the oxygen bridge is intact, give red to purple shades of varying intensities with Marquis' reagent (6), formalin in conc'd H_2SO_4 (7). In contrast, III and IV give blue-green colors with this reagent and resemble dihydrothebainone (V) in this respect. This point was unequivocally demonstrated by methylation of the dihydro derivative (IV) with diazomethane, resulting in the isolation of dihydrothebainone (V). A single attempt to convert III to the known thebainone, (8) VI, with diazomethane resulted in resins. This may not be surprising in view of the known reactivity of α,β-unsaturated ketones towards diazomethane. Additional confirmation for the *o*-diphenol structure of III and IV may be deduced from the sensitivity of the compounds to air in the presence of alkali, IV being more sensitive than III.

The optical activities of III and IV are in good agreement with the assigned structures, the $[\alpha]_D$-values having the expected similarity with those of the respective methyl ethers, VI and V.

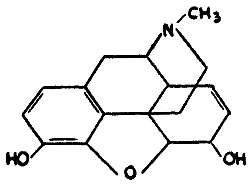
	III	VI (9a)	IV	V (9b)
$[\alpha]_D$	−34.3°	−42.5°	−68°	−72.5°

It may be interesting to speculate upon the mechanism by which this O-desmethylthebainone (III) may be formed. Formal analogies to such oxygen-bridge cleavages are available, but, in all probability, cannot be compared to the situation here described. Thus, codeine methyl ether VIIa can be transformed to thebainone methyl enolate VIIIa by the action of sodium alcoholate (10) and α-ethylthiocodide (VIIb) is similarly isomerized to β-ethylthiocodide (VIIIb) (10).

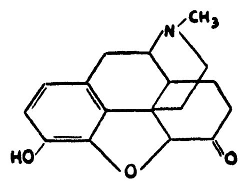
The same reaction with morphine should result in III (as its enol form), but opposed to this is the observation (10) that codeine does not undergo this transformation. In any case these reactions (VII → VIII) are promoted by alkali whereas the formation of III takes place in acid solution.

The fact that a hydrogenation-dehydrogenation catalyst is necessary for the transformation leads us to suggest a hypothesis based on intra- and inter-molecular hydrogenation. Under all conditions examined both III and dihydromorphinone II are formed in varying proportions, dependent on the type and quantity of catalyst. The highest yield of III was obtained in the presence of a large amount of 10% palladium on charcoal catalyst, the proportion of dihydro-

morphinone increasing and that of III decreasing as the quantity of catalyst was decreased. When a less active palladium-black catalyst was used, the yield of



I



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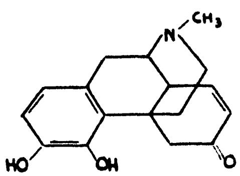
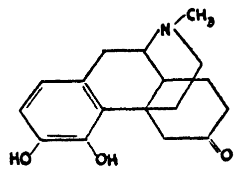
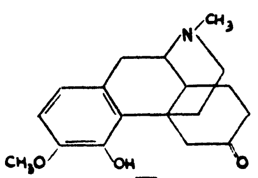


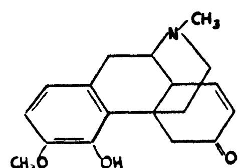
III



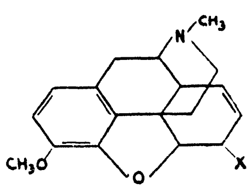
IV



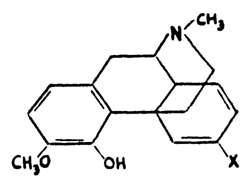
V



VI

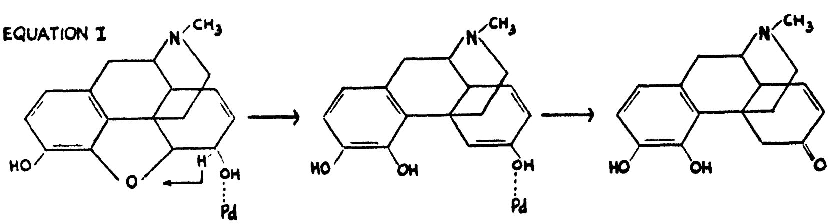


VII a, $X = OCH_3$
b, $X = -SC_2H_5$



VIII a, $X = -OCH_3$
b, $X = -SC_2H_5$

EQUATION I



III was diminished, and a certain amount of dihydromorphine was obtained, in all probability by reduction of morphine with hydrogen occluded in the catalyst. This possibly indicates that in the presence of a small amount of catalyst many morphine molecules are adsorbed at a single active center, favoring an intermolecular hydrogen exchange resulting in dihydromorphinone, whereas in the presence of a large quantity of catalyst the possibility of single morphine molecules being adsorbed at single active centers would be favored (Equation I).

The electron deficient catalyst, sharing the free electrons of the hydroxyl oxygen would presumably mobilize the hydrogen on carbon atom 6 in a fashion analogous to the function of the aluminum in the Meerwein–Ponndorf–Verley reduction. The availability of an adjacent electron-rich center, the oxygen bridge, would, on this assumption, provide a proton-accepting atom quite similar to that furnished by the carbonyl group in the Meerwein–Ponndorf–Verley reduction. A similar case may be cited in the observations of Adkins and Folkers (11) on the thermal disproportionation of 2,2-dimethyl-3-butene-1-ol over alumina. In this case the products were 2,2-dimethyl-3-butene-1-al and 2,2-dimethylbutene.

Addition to proof, received Feb. 4, 1949: Further experimental work carried out since submission of this paper, has shown that codeine is converted in part to thebainone under similar conditions.

ACKNOWLEDGMENT

We wish to acknowledge the assistance of J. Braude in carrying out some of the experiments and of Joseph E. Machurek in the preparation of the drawing. We are indebted to Dr. L. F. Small for a stimulating discussion of the findings herein reported.

EXPERIMENTAL

O-desmethylthebainone (*III*). Fifty g. of morphine hydrochloride trihydrate was dissolved in 250 cc. of water in a one-liter flask, 6.5 cc. of 2 *N* hydrochloric acid and 60 g. of 10% palladium on charcoal catalyst[4] was added. The flask was flushed free of air with nitrogen and placed in an electrically heated shaking apparatus. The temperature was raised to 80° without shaking, and the reaction mixture was shaken at this temperature, in nitrogen atmosphere, for seventeen hours. At the end of the shaking period the mixture was allowed to cool to room temperature. The solution was freed of catalyst and the catalyst washed with water. The combined filtrate and washings were transferred to a separatory funnel with 380 cc. of chloroform. While the two immiscible layers were being agitated by a rapid stream of nitrogen bubbles, 105 cc. of 2 *N* ammonium hydroxide was added dropwise to the mixture. A heavy precipitate, which created a nearly inseparable interphase layer, formed. The mixture was filtered by suction, the precipitate was washed thoroughly on the funnel with chloroform, and the aqueous phase of the filtrate was extracted further with chloroform. From the combined chloroform extracts, dihydromorphinone was isolated by concentration, yield 5.3 g., 14%.

The filtered O-desmethylthebainone (III) was dried *in vacuo*, and was thus obtained as a gray-to-brown amorphous-appearing powder. The product was purified by several recrystallizations from pyridine at steam-bath temperature in a nitrogen atmosphere. At this temperature the compound requires approximately 30 volumes of the solvent; m.p. 220–221° (dec.) in a sealed capillary, bath preheated to 200°. The analytical sample was dried over boiling acetone at 2 mm.

Anal.[5] Calc'd for $C_{17}H_{19}NO_3$: C, 71.55; H, 6.71; N, 4.93.

Found: C, 71.17; H, 6.74; N, 4.92, 5.03.

The compound is moderately soluble in ethanol, slightly soluble in benzyl alcohol, and

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[4] Obtained from Baker Platinum Works, Newark, N. J.

[5] Microanalyses by Mr. W. Saschek, Columbia University, and Oakwold Labs., Fairfax, Va.

very slightly soluble in benzene, chloroform, heptane, acetone, ethyl acetate, or dioxane. Samples obtained from several of the above solvents exhibited the same melting point and color reactions (listed below) as that obtained from pyridine.

O-desmethylthebainone (III), in alcoholic suspension, gives a purple color with a small amount of ferric chloride solution (approx. 10%), which becomes blue-green to green with more of the reagent. We observed that dihydrothebainone (V) behaves in a similar way. With Marquis' reagent the substance produces a blue-green color of low intensity. The color reaction with alkali has already been described; optical rotation: $[\alpha]_D^{24}$ −34.3° (10% acetic acid, *c*, 3.62).

Isolation via the hydrochloride. The aqueous filtrate from a reaction, similar to the one leading to the above product, which started with 36 g. of morphine hydrochloride trihydrate and 1.8 g. of 10% palladium-charcoal catalyst, was evaporated to dryness under reduced pressure in a stream of nitrogen. The residue was converted to a crystalline mass by suspending in 3 successive 20-cc. portions of ethanol which were evaporated, *in vacuo*, in turn. The resulting powder was extracted with four successive 100-cc. portions of boiling ethanol, leaving dihydromorphinone hydrochloride undissolved. The alcoholic filtrates, on partial evaporation, yielded 16.4 g. of hydrochloride, from which O-desmethylthebainone, m.p. 216° (dec.) was isolated. Fractional recrystallization of the hydrochloride from ethanol and conversion to the free base gave material of identical melting point from the least soluble, intermediate, and most soluble fractions.

Oxime. The free base III (10 g.), treated with 10 g. of hydroxylamine hydrochloride in 100 cc. of water on the steam-bath for 30 minutes, yielded, on cooling, 7.0 g. of well-crystallized oxime hydrochloride. This salt exhibited a variety of melting points (243°, 265°, 274°) for the various fractions isolated from recrystallizations in methanol. These all yielded identical bases upon treatment with sodium bicarbonate, m.p. 274–279. The free base isolated, by sodium bicarbonate treatment, from the mother liquor of the oximation reaction mixture also had the same m.p. No suitable solvent for recrystallization of the oxime base was found. A crude sample was submitted to analysis.

Anal. Calc'd for $C_{17}H_{20}N_2O_3$: N, 9.33. Found (Kjeldahl): N, 8.97.

Thiosemicarbazone hydrochloride. O-desmethylthebainone (III) (2.85 g.) was brought into solution in 15 cc. of water by addition of the calculated quantity of 2 *N* hydrochloric acid, and then treated on the steam-bath with 0.91 g. of thiosemicarbazide. The thiosemicarbazide dissolved rapidly, but the solution was allowed to remain at steam-bath temperature for two hours. Some crystallization occasionally took place during this period, and was completed by cooling the mixture in an ice-bath. The filtered solid was washed with ice water, yield 2.85 g., m.p. 217°. The yellow platelets, obtained by recrystallization from water or methanol, melted at 219–220°. The color could not be removed by the use of charcoal or sodium hydrosulfite.

Anal. Calc'd for $C_{18}H_{23}ClN_4O_2S$: N, 14.19; S, 8.10.
Found: N, 14.03, 13.95; S, 8.04, 7.80.

The thiosemicarbazone base, obtained by treatment of a warm aqueous solution of the hydrochloride with sodium bicarbonate, was a yellowish, apparently amorphous powder; m.p. 210° (dec.). It could not be recrystallized from a variety of solvents and was not further investigated.

Diacetyl derivative. Ten grams of O-desmethylthebainone (III) was suspended in 80 cc. of acetic anhydride at room temperature. The solid dissolved in about ten minutes, and the brown solution was allowed to remain at room temperature for two hours. It was then poured into 160 cc. of water and shaken until the mixture became homogeneous. The subsequent work-up was carried out within an hour, since a similar reaction mixture, allowed to stand overnight, yielded only recovered III. The solution was transferred to a separatory funnel containing 100 cc. of chloroform, and was made alkaline to phenolphthalein with 28% ammonia while the two layers were thoroughly mixed with a rapid stream of nitrogen bubbles. The aqueous layer was extracted with four additional 100 cc. portions of chloroform, the combined chloroform extracts were dried with sodium sulfate, and treated

simultaneously with Darco G-60. The filtered solution was evaporated to dryness *in vacuo*, leaving an amorphous residue. Upon standing at room temperature, under nitrogen, for two days it became crystalline. This product was recrystallized from chloroform-ether mixture and obtained as needles, m.p. 181–184°; yield 5.1 g. (40%). For analysis it was recrystallized from five volumes of ethanol, but in spite of the use of additional charcoal, was obtained as light tan crystals, m.p. 183–184°.

Anal. Calc'd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79.
Found: C, 68.43; H, 6.52; N, 3.85.

M.W. Calc'd, 369.4. Found: (a) Rast, (camphor): 318 (0.0398 gm. in 0.4780 gm. camphor: $-\Delta$ T = 10.5°). (b) Cryoscopic in benzene: 0.2531 gm. in 36.15 gms. benzene: $-\Delta$ T (avg.) = 0.104°. M.W. = 348.

This diacetyl derivative produces no color with ferric chloride in ethanol solution. It sublimes readily at 110–115° and 3×10^{-4} mm.

O-desmethyldihydrothebainone. A solution of 25.4 g. of III in 200 cc. of water plus a slight excess over the stoichiometric quantity of 2 *N* hydrochloric acid was shaken with hydrogen and 1.5 g. of 10% palladium-charcoal until hydrogen uptake stopped. The reaction consumed 0.95 equivalent of hydrogen.

The solution was filtered and concentrated *in vacuo* to incipient crystallization. Chilling, at this point, produced a crystalline magma, which was filtered, washed twice with ice-water, and dried *in vacuo* over phosphorus pentoxide; yield 21 g., m.p. very unsharp at 165–170°.

The base was obtained by solution of the above hydrochloride in 160 cc. of lukewarm water, containing a small amount of sodium hydrosulfite, and neutralization to phenolphthalein with ammonia, 1:1. O-desmethyldihydrothebainone precipitated as a heavy white powder, which was readily soluble in excess ammonia. The mixture was chilled and filtered. The filter-cake was washed with cold water and then dried *in vacuo* over phosphorus pentoxide; yield 16.6 g., m.p. 274°.

An additional quantity of the base was obtained from the above aqueous mother liquors upon standing for several days after addition of sodium bicarbonate solution.

Difficulty was encountered in the recrystallization of this material for analysis, but samples that gave consistent and concordant results were finally obtained by recrystallizing first from pyridine (10–12 volumes) and then from anisole (30 volumes) and drying over boiling Methyl Cellosolve at 2 mm.

Anal. Calc'd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87.
Found: C, 71.16, 71.53; H, 6.74, 6.95; N, 5.22, 4.91.
$[\alpha]_D^{24}$ —68° (*c*, 1.264 in 10% acetic acid)

The compound is readily soluble in benzyl alcohol at room temperature, and moderately soluble in boiling acetone. An aqueous suspension of the dihydro compound becomes brown with great rapidity, and addition of alkali produces a light red solution. If the addition of alkali is done in the presence of sodium hydrosulfite a colorless solution results, which, however, becomes brown in a short time.

Addition of a few drops of 10% ferric chloride solution to an aqueous or alcoholic suspension of the dihydro compound yields a purple color which can be changed to green by addition of more reagent.

With Marquis' (7) reagent an intense blue-to-green color is produced.

O-desmethyldihydrothebainone oxime hydrochloride. Purified IV (1 g.) was heated on the steam-bath with a solution of one gram of hydroxylamine hydrochloride in 25 cc. of water for 30 minutes. The solution was chilled in an ice-bath and the flask scratched with a glass rod, thereby inducing crystallization. This oxime hydrochloride was so sparingly soluble in boiling methanol that a true recrystallization could not be achieved, but since the material which was obtained upon crystallization from the mother liquors of digestion with boiling methanol had the same m.p. as the digested residue, m.p. 318–320° (dec.), the latter was considered sufficiently pure for analysis. The analytical data check best for a compound with $1.5H_2O$, without excluding those with either $1H_2O$ or $2H_2O$.

The N/HCl ratio is sufficiently close to two to leave no doubt as to the identity of this compound.

Found: N (Kjeldahl) 7.57, 7.58; HCl, 10.02. Ratio N/HCl = 1.97.

Calculated for

	$C_{17}H_{22}ClN_2O_3$	$1H_2O$	$1.5H_2O$	$2H_2O$
N	8.28	7.85	7.66	7.47
HCl	10.77	10.22	9.97	9.74.

O-desmethyldihydrothebainone thiosemicarbazone hydrochloride. O-desmethyldihydrothebainone (2.45 g.) was added to a mixture of 0.8 g. of thiosemicarbazide in 15 cc. of water and 8.5 cc. of *N* hydrochloric acid. This was heated on the steam-bath for two hours. The resulting brown solution was cooled in an ice-bath, and seeded. The crystalline magma was refrigerated overnight, filtered, washed with ice-water, and dried *in vacuo* over phosphorus pentoxide. It was thus obtained as a colorless, microcrystalline powder, yield 2.7 g. (79%). This salt was recrystallized from four volumes of boiling water with a recovery of about 75%. The product thus obtained showed no sharp melting point, starting to sinter and discolor at about 210° and decomposing at about 250°, this latter temperature depending upon the rate of heating. The salt is also soluble in ethanol.

Anal. Calc'd for $C_{18}H_{25}ClN_4O_2S$: N, 14.11. Found: N, 14.06, 14.27.

Sulfur determinations were made but came out inexplicably high, calc'd 8.08%; found, 9.55, 9.42%. However, the excellent agreement of the nitrogen values, and the concordance of the absorption spectrum with that expected can leave little doubt as to the identity of the compound.

The corresponding base was isolated by treatment of the mother liquors of the original reaction mixture with sodium bicarbonate solution. In this manner, 0.3 g. of base was obtained as globular aggregates of very short needles, m.p. unsharp at 260–280° (dec.). It was very soluble in pyridine, boiling ethanol, and anisole, but none of these, nor any of several other solvents tried, proved to be appropriate for recrystallization, and the base was not further investigated.

Methylation of O-desmethyldihydrothebainone; dihydrothebainone. To a solution of 8.61 gms. (0.03 mole) of IV in 180 cc. of dry benzyl alcohol an ethereal solution of diazomethane[6] (12) in slight excess of one equivalent, was added, portion-wise, in about twenty minutes. Nitrogen was evolved, but the usual end-point, disappearance of the yellow color, could not be noted due to the formation of a light red color. After standing at room temperature for about 30 minutes, the solution was shaken with 100 cc. of 1:10 hydrochloric acid. The separated benzyl alcohol layer was then washed three times with small portions of acidified water, which were combined with the original aqueous extracts. The aqueous solution was then washed five times with ether to remove the dissolved benzyl alcohol.

The aqueous solution was adjusted to approximately *p*H 9 with ammonia and the resulting milky dispersion was extracted with four portions of chloroform. After drying over sodium sulfate, the chloroform was evaporated to dryness *in vacuo* to yield a glassy brown residue. This could be induced to crystallize by treatment with a small volume of cold acetone. However, it was dissolved in hot acetone and the solution treated with charcoal; the cooled filtrate, upon seeding with authentic dihydrothebainone, deposited a heavy crop of crystals. After filtration, washing with ice-cold acetone, and drying, the yield was 1.3 g.; m.p. 132–133°.

The literature lists a variety of melting points, ranging from 133° to 150°, for dihydrothebainone. In our hands, authentic samples of dihydrothebainone, recrystallized from acetone, melt around 145°. Two additional recrystallizations, from acetone, of the material isolated in this experiment gave a sample that melted at 144–146° after sintering at 138°. Mixed melting point of an authentic sample (m.p. 142–145°) with this material was undepressed, sintering at 142° and melting at 144–146°.

[6] Dry benzyl alcohol was substituted for the recommended cyclohexanol.

Confirmation of this identification was obtained by comparison of the oxime base and oxime hydrochloride with the same derivatives prepared from authentic dihydrothebainone.

	MELTING POINTS		
	This Expt.	Authentic Deriv.	Mixture
Oxime Base	245°	244.5–245°	244.5–245°
Oxime HCl	311°	319°	314°

The product of this experiment gave, in alcoholic solution, with ferric chloride, a characteristic green color, indistinguishable from that similarly produced by authentic dihydrothebainone.

An additional quantity (2.7 g.) of this same product was isolated from the original mother liquors by conversion to the alcohol-insoluble hydrochloride, using alcoholic hydrogen chloride.

Hydrogenolysis of O-desmethylthebainone oxime. Two and one-half g. of O-desmethylthebainone oxime was dissolved in a mixture of 10 cc. of glacial acetic acid and 40 cc. of water. The solution was shaken with hydrogen in the presence of 0.15 g. of 10% palladium-charcoal catalyst until absorption stopped. This corresponded to 2.18 moles of hydrogen.

After completion of the absorption and removal of the catalyst, a small portion of the filtrate was treated with excess sodium hydroxide solution and ammonia was demonstrated by odor and blueing of red litmus paper by the evolved vapors.

The remainder of the filtrate was evaporated *in vacuo* to a syrup, which was dissolved in warm ethanol. Cooling this solution resulted in the crystallization of a presumed acetate. This was filtered, washed with ice-cold alcohol, and dried *in vacuo* over phosphorus pentoxide. It melted unsharply at 187–189° when immersed in a bath at 160°; yield 0.7 g. More of this same material was obtained by concentration of the alcoholic mother liquors and precipitation with ether. This product was converted to an amorphous base, unsharp m.p. about 180°, by treatment of its aqueous solution with excess sodium bicarbonate solution.

Since this material was very soluble in chloroform and ethyl acetate, due possibly to excessive contamination with by-products, it was treated with hydroxylamine hydrochloride in water. Upon working up as described for O-desmethyldihydrothebainone oxime hydrochloride (above), material of m.p. 320° (unsharp) with preliminary sintering at 310° was obtained. By digestion with hot ethanol a crystalline sample of m.p. 315°, undepressed by admixture with an authentic sample, was obtained.

SUMMARY

The isomerization of morphine to O-desmethylthebainone is described.

Chemical and spectroscopic evidence for the structure of this compound is presented.

A mechanism for this isomerization under the influence of a palladium catalyst, based on intramolecular dehydrogenation, is suggested.

RICHMOND HILL 18, N. Y.

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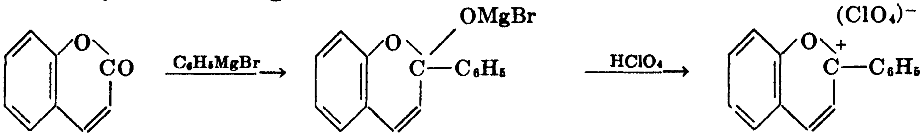
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF INDIANA UNIVERSITY]

ISOBENZOPYRYLIUM SALTS. I. PREPARATION AND REACTIONS OF 1-PHENYL-2-BENZOPYRYLIUM SALTS[1]

R. L. SHRINER,[2] H. W. JOHNSTON,[3] AND C. E. KASLOW

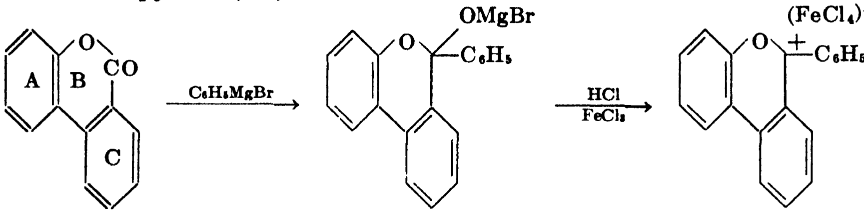
Received June 17, 1948

One of the general methods for preparing 1-benzopyrylium salts (II) consists in treating coumarin (I) (or substituted coumarins) with one mole of the Grignard reagent under conditions such that 1,2 addition to the carbonyl group occurs and then reaction of the adduct or the pyranol with a strong acid (1) as shown by the following:



I II

In 1908 Decker and Felser (2) prepared the dibenzopyrylium salt (IV) from the dibenzo-α-pyrone (III).



III IV

Now the lactone (III) may be regarded as a coumarin (Rings A + B) or as an isocoumarin (Rings C + B). Hence, the question arises whether isocoumarin itself (V) would undergo similar reactions and lead to isobenzopyrylium salts (VII).

A study of this possibility has shown that the above reactions do occur and that the isobenzopyrylium perchlorate (VII) can be isolated as golden-orange crystals. To establish the structure of this salt it was subjected to ozonolysis and *o*-benzoylbenzoic acid (IX) isolated. When VII was heated with ammonium hydroxide and ammonium chloride in a sealed tube at 160°, 1-phenylisoquinoli n (VIII) was formed.

This last reaction parallels the behavior of unsubstituted 2-benzopyrylium ferrichloride (XI) which is the only other example of an isobenzopyrylium salt which could be found in the literature. Blount and Robinson (3) oxidized *trans*-1,2-hydrindanediol (X) with lead tetraacetate and treated the product with ferric chloride and hydrogen chloride to produce a compound assigned the structure XI, since ammonia converted it to isoquinoline (XII).

[1] From a thesis submitted by H. W. Johnston to the Graduate School of Indiana University in partial fulfilment of the requirements for the Ph.D. in chemistry.

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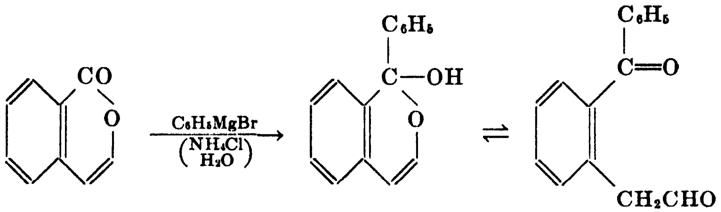
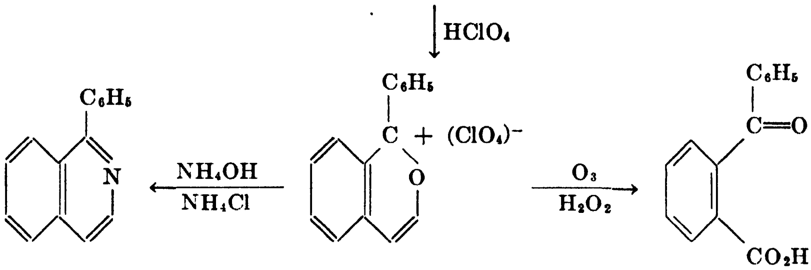
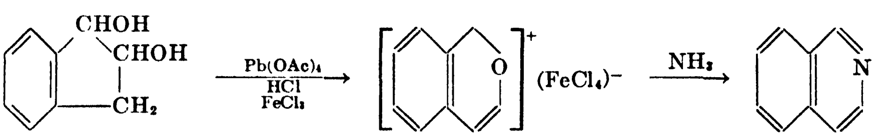


V VIa VIb



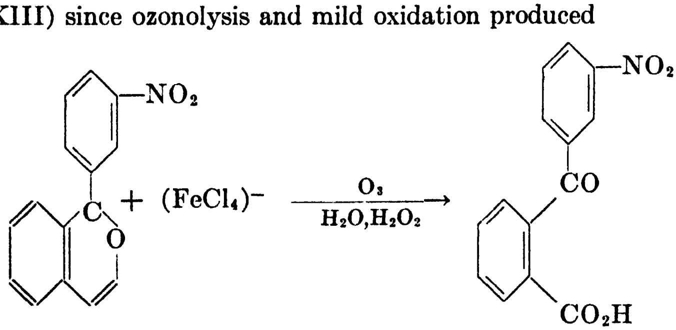
VIII VII IX



X XI XII

In the present work, the intermediate carbinol VIa could not be isolated in the pure state. It is a hemiketal and is probably in equilibrium with the structure VIb which was indicated by the fact that treatment of this intermediate product with phenylhydrazine gave a compound whose analysis indicated it was the *bis*-phenylhydrazone of VIb.

Additional evidence for the carbonium structure shown by formula VII was obtained by nitration with nitric and sulfuric acids at 45°. A mononitro derivative was obtained both as the perchlorate and as the ferrichloride. The structure of the latter was established as 1-(3-nitrophenyl)-2-benzopyrylium ferrichloride (XIII) since ozonolysis and mild oxidation produced



XIII XIV

o-(3-nitrobenzoyl)benzoic acid (XIV). The latter was characterized by comparison with a known sample prepared by nitration of *o*-benzoylbenzoic acid

according to the procedures of Lang (4) and Ranier (5). No nitration products could be found in which a nitro group had entered the benzo nucleus. Nitration experiments at higher temperatures and longer times led to complete decomposition and no di- or tri-nitro derivatives could be obtained.

These nitration results parallel the results obtained by LeFevre (6) in nitration of 2-phenyl-1-benzopyrylium perchlorate and by Shriner and Moffett (7) in nitration of 1,2-diphenyl-1-benzopyrylium perchlorate.

The results indicate that the 1-carbon atom in the salt (VII) carried a positive charge since the nitro group entered the position *meta* to it. The ozonolysis experiments indicate that the heterocyclic ring is retained in both VII and XIII since opening of this ring followed by mild oxidation with hydrogen peroxide would have given substituted phenylacetic acids.

It is evident that a considerable number of theoretically possible resonance structures could be written for these isobenzopyrylium salts. The structure shown by VII represents only one of the possibilities. It has been selected as a useful working carbonium ion structure compatible with: (a) its formation from the intermediate carbinol (VIa) by a double decomposition reaction with perchloric acid, (b) entrance of the nitro group in the 3-position of the 1-phenyl group and (c) the selective ozonolysis to give *o*-benzoylbenzoic acid which indicates the double bond in the heterocyclic ring is in the 3,4-position. This does not mean that it is the only structure but that it is the one involved in these particular chemical properties. Undoubtedly one of the reasons why these salts can be isolated and are so stable is due to resonance with all the other possibilities.

EXPERIMENTAL PART

1-Phenyl-2-benzopyrylium perchlorate (VII). To a solution of 21 g. (0.14 mole) of isocoumarin (8) in 100 ml. of absolute ether cooled to 0° was added 0.13 mole of phenylmagnesium bromide in 100 ml. of absolute ether. After stirring for 5 hours the yellow complex was decomposed by addition of 300 ml. of 20% ammonium chloride solution. The ether layer containing the carbinol (VIa) was separated, washed with water, and dried with magnesium sulfate. It was cooled to 0° and a solution of 15.0 g. of 70% perchloric acid in 30 ml. of acetic anhydride and 150 ml. of absolute ether added dropwise with vigorous stirring. The yellow perchlorate was removed by filtration, washed with dry ether and recrystallized three times from anhydrous ethylene chloride. The golden-orange crystals then melted constantly at 210–211° (with decomposition) and amounted to 9 g. (21%).

Anal. Calc'd for $C_{15}H_{11}ClO_5$: ClO_4, 32.43. Found: ClO_4, 32.58.

Ozonolysis of 1-phenyl-2-benzopyrylium perchlorate. A solution of 0.8 g. of the above salt in 50 ml. of ethylene chloride was treated with 3% ozone for 2 hours. After removal of the solvent under reduced pressure, the ozonide was decomposed with 10 ml. of water and 1 ml. 30% hydrogen peroxide. This mixture was extracted with ether and the ether solution extracted with 10% sodium carbonate solution. Acidification of the latter gave a red gum which was removed by filtration and the filtrate was chilled in an ice-box. The solid precipitate, after recrystallization from water-methanol mixture (3:1) gave white crystals of the hydrate of *o*-benzoylbenzoic acid; m.p. 92–93°. Recrystallization from benzene gave the anhydrous acid; m.p. 125–126°. When mixed with a known sample no depression of the melting point occurred. Kunckell and Knigge (9) report 93–94° for the hydrate and 127° for the anhydrous acid.

Bis-phenylhydrazone of o-benzoylphenylacetaldehyde (VIb). Evaporation of the ether from a solution of the carbinol (VIa) obtained as described above, gave an oil which could

not be crystallized or purified by distillation. However, the oil was dissolved in dioxane and refluxed with a solution of 2.9 g. of phenylhydrazine hydrochloride and 5.5 g. of sodium acetate in 100 ml. of water for one hour. After cooling and standing for some time, yellow crystals separated. After three recrystallizations from 95% ethanol there was obtained 0.3 g. of pale yellow needles melting constantly at 197–199°.

Anal. Calc'd for $C_{27}H_{24}N_4$: N, 13.86. Found: N, 14.15; 13.98.

1-Phenylisoquinoline. A mixture of 0.2 g. of 1-phenyl-2-benzopyrylium perchlorate, 5 ml. of concentrated ammonium hydroxide, and 0.1 g. of ammonium chloride was heated in a sealed tube at 160° for one hour. After cooling and opening the tube, the contents were boiled to drive off the excess ammonia and then clarified by adding a few ml. of ethanol. Upon cooling the solution, a tan powder of m.p. 90–95° was obtained. It was dissolved in 10 ml. of hot alcohol, decolorized with Norit, and the filtrate diluted with water until turbid and then cooled in an ice-bath. The product was again recrystallized from 50% ethanol and was obtained as white needles melting at 93–94°.

Rosenmund, Nothnagel, and Riesenfeld (10) reported the melting point 94° for 1-phenylisoquinoline; Späth, Berger, and Kuntara (11) reported 95–96° from petroleum ether; Ziegler and Zieser (12) reported 97° from toluene-petroleum ether; and Rodionov and Yavorskaya (13) recorded 94–95° from alcohol.

1-(3-Nitrophenyl)-2-benzopyrylium perchlorate. One gram of 1-phenyl-2-benzopyrylium perchlorate was dissolved in a mixture of 5 ml. of concentrated nitric acid and 5 ml. of concentrated sulfuric acid at 45°. The reaction mixture was held at this temperture for five minutes and then poured onto 25 g. of cracked ice. The yellow mixture was extracted twice with 25 ml. of ether. The ether solution was washed three times with small portions of cold water and dried over magnesium sulfate.

The magnesium sulfate was removed by filtration and washed twice with small portions of dry ether which were added to the filtrate. The ether mixture was chilled in an ice-salt bath and 0.28 ml. (0.47 g., 0.00326 mole) of 70% perchloric acid in 5 ml. of acetic anhydride and 25 ml. of dry ether was added. A yellow powder was obtained which decomposed at 200°. The product was dissolved in about 15 ml. of warm pure nitromethane. Dry ether was added dropwise until fine orange needles of 1-(3-nitrophenyl)-2-benzopyrylium perchlorate precipitated. The purification procedure was repeated three times until the product melted constantly at 240.5° with decomposition. The yield was 0.5 g. (43%).

Anal. Calc'd for $C_{15}H_{10}ClNO_7$: ClO_4, 28.38. Found: ClO_4, 28.17.

1-(3-Nitrophenyl)-2-benzopyrylium ferrichloride (XIII). Two grams (0.0065 mole) of 1-phenyl-2-benzopyrylium perchlorate was dissolved in a mixture of 10 ml. of concentrated nitric acid and 10 ml. of concentrated sulfuric acid at 45°. The reaction mixture was held at this temperature for five minutes and then poured onto 25 g. of cracked ice. The yellow powder was collected on a filter, washed with distilled water, and dissolved in 70 ml. of warm concentrated hydrochloric acid. An excess of ferric chloride (also dissolved in concentrated hydrochloric acid) was added. The solid yellow product was collected on a filter and recrystallized twice from glacial acetic acid. Bright yellow needles, m.p. 138° (decomp.) were obtained; yield 1 g. (34%).

Anal. Calc'd for $C_{15}H_{10}Cl_4FeNO_3$: N, 3.11; Fe, 12.42.
Found: N, 3.00; Fe, 12.34.

Ozonolysis of 1-(3-nitrophenyl)-2-benzopyrylium ferrichloride. One gram of 1-(3-nitrophenyl)-2-benzopyrylium ferrichloride was dissolved in 500 ml. of glacial acetic acid and subjected to a stream of 3% ozone for 3 hours. The solvent was removed on the water-bath under reduced pressure and about 50 ml. of distilled water and 1 ml. of 30% hydrogen peroxide were added. The mixture was heated to boiling, cooled, and acidified with hydrochloric acid. The solution was extracted with three 50-ml. portions of ether. The ether solution was extracted with two 25-ml. portions of 10% sodium carbonate and the aqueous portion was then removed and acidified with hydrochloric acid. A milky oil appeared which solidified upon chilling in the ice-box overnight. A pale yellow powder was obtained which was recrystallized several times from dilute acetic acid. Pale yellow needles, m.p. 181.5–

183.5° were obtained. This compound was identified as 2-(3-nitrobenzoyl)benzoic acid since it did not depress the melting point of an authentic sample prepared by the nitration of *o*-benzoylbenzoic acid following the procedure described by Lang (4) and Ranier (5). The melting point of 2-(3-nitrobenzoyl)benzoic acid is quite different from the other known isomeric nitrobenzoylbenzoic acids described by Ranier (14) and by Lawrence (15).

Properties and analysis of organic perchlorates. Since perchloric acid may react violently with certain organic compounds, the preparation and recrystallization of the benzopyrylium and isobenzopyrylium perchlorates should always be carried out behind laminated safety glass shields. It will be noted that the yields of some of the perchlorates are rather low. Undoubtedly more of the compounds are present in the filtrates but the concentration of these is rather hazardous and is not recommended. The various carbonium perchlorates are crystalline, non-hydroscopic solids which are stable under ordinary conditions. They possess characteristic and reproducible melting points with more or less decomposition depending on the particular compound. When heated above their melting points the organic perchlorates decompose vigorously—sometimes explosively. For this reason, it is usually impossible to obtain good analyses for carbon, hydrogen, or nitrogen since the combustion cannot be easily controlled.

The analysis of the organic perchlorates may be accomplished by treatment of an alcoholic solution of the sample with a solution of potassium acetate. The potassium perchlorate is collected on a filter, dried, and weighed. However, the appreciable solubility of potassium perchlorate in the aqueous alcohol medium, makes it necessary to determine and apply a correction. The best method for the analysis of organic perchlorates utilizes precipitation of the perchlorate anion by tetraphenylarsonium chloride (16) from a methanolic solution of the sample. The tetraphenylarsonium perchlorate is quite insoluble and is collected on a sintered glass filter, dried at 105° and weighed. This reagent is more accurate since the quaternary perchlorate is quite insoluble in methanol and the factor $ClO_4/(C_6H_5)_4AsClO_4 (= 0.2060)$ is very favorable. This method is an application of the procedure of Willard and Smith (17) for the analysis of inorganic perchlorates. The isobenzopyrylium perchlorates described in this paper were analyzed by this method.

SUMMARY

1-Phenyl-2-benzopyrylium perchlorate was produced by the action of phenylmagnesium bromide on isocoumarin followed by treatment with perchloric acid. Nitration of this salt formed 1-(3-nitrophenyl)-2-benzopyrylium perchlorate as shown by conversion to *o*-(3-nitrobenzoyl)benzoic acid.

BLOOMINGTON, IND.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

A STUDY OF THE SYNTHESIS OF VINYLPYRIMIDINES[1]

CHARLES C. PRICE AND JACK ZOMLEFER[2]

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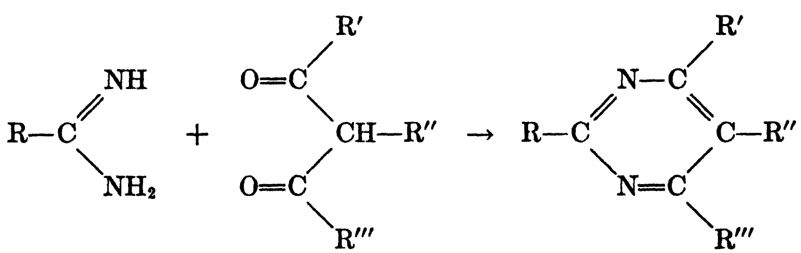
Since the preparation and characterization of vinylpyrimidines seemed a problem of possible practical and theoretical interest, an investigation aimed toward this end was considered desirable. Although to date no monomeric vinylpyrimidine has been isolated, the results appear of some significance and are therefore reported here at this time.

It would appear that the direct condensation of 2- or 4-methylpyrimidine with formaldehyde might be a logical approach. Since these simple methylpyrimidines are difficult to prepare and work with, an alternative approach was chosen involving direct synthesis of a pyrimidine ring system containing a vinyl group or a group easily transformable to a vinyl group.

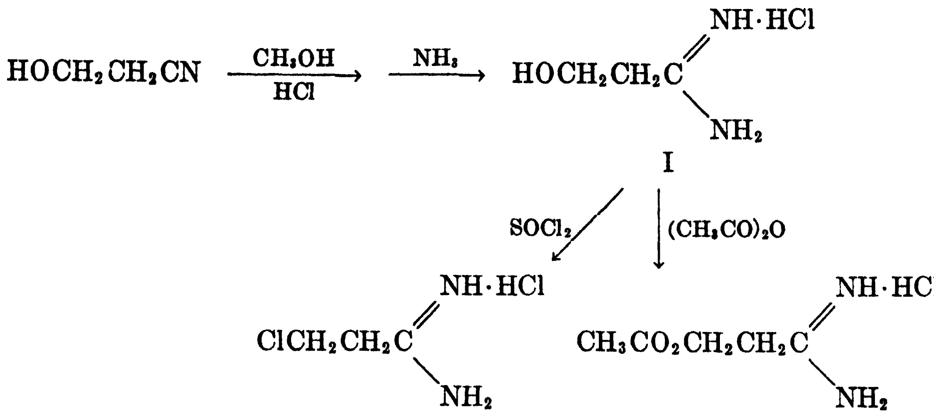


Such a classical pyrimidine synthesis, in which any one of the R groups could be vinyl (or β-chloroethyl, β-hydroxyethyl or β-acetoxyethyl), the remainder preferably hydrogen or alkyl, might present a rather direct approach to a vinylpyrimidine. Experiments on the approach in which R is the potential vinyl group were most thoroughly investigated, since the starting materials seemed the most readily available.

The first objective was the synthesis of the desired amidines, acrylamidine or 3-hydroxy-, 3-chloro- or 3-acetoxy-propionamidine. Of these, only the hydroxy compound could be prepared from the corresponding nitrile, ethylene cyanohydrin, by the usual amidine preparation of Pinner and Klein (1). The 3-acetoxy and 3-chloro derivatives were prepared from the 3-hydroxypropionamidine.

[1] Abstracted from a Ph.D. thesis presented to the Graduate School of the University of Notre Dame.

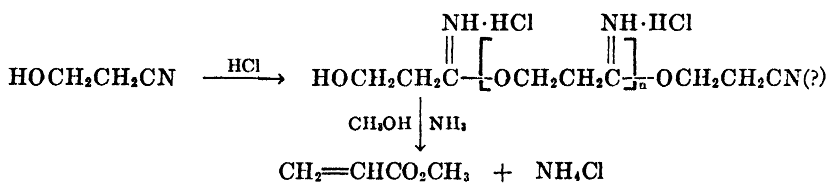
[2] General Tire and Rubber Company Fellow, 1946–1947; American Cyanamid Company Fellow, 1947–1948.



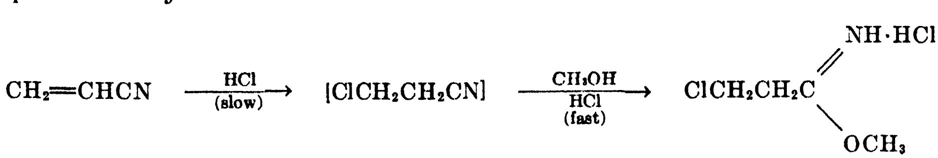
III II

These amidine hydrochlorides were all extremely hygroscopic and difficult to handle and purify.

Incidentally, attempts were made to prepare a polyimidic ester from ethylene cyanohydrin by omitting methanol, relying on the hydroxyl group already present in the nitrile. The evidence indicated that the polyimidic ester was formed but decomposition with methanolic ammonia proceeded to methyl acrylate and ammonium chloride.



On treatment of acrylonitrile with two equivalents of hydrogen chloride in methanol, methyl 3-chloropropionimidate hydrochloride was formed in nearly quantitative yield.



IV

When only one equivalent of hydrogen chloride was used, only half the theoretical amount of IV was obtained. In either case, the reaction required several days. When 3-chloropropionitrile was used as starting material, the reaction required only one equivalent of hydrogen chloride and proceeded to completion within two hours. From these data, which indicate a rather remarkable difference in the reactivity of the nitrile group in acrylonitrile and 3-chloropropionitrile, it appears that conjugation of the nitrile triple bond with the carbon-carbon

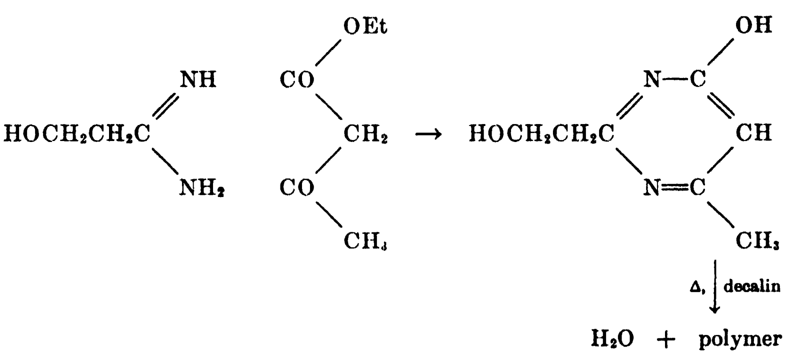
double bond (a) decreases its reactivity toward addition, and (b) allows 1,4-addition to occur.

Treatment of the imidate IV with ammonia produced an amorphous polymeric product and ammonium chloride; it seems evident that the chlorine atom is too reactive, presumably undergoing replacement both by ammonia and by any amidine which may be formed. It was, however, possible to convert the imidate IV to 3-chloropropionamide by cautious hydrolysis.

Attempts to convert 3-acetoxypropionitrile to the imidate and thence to the amidine failed, apparently due to the ready transesterification with methanol, converting the latter to methyl acetate, the former to ethylene cyanohydrin.

The condensation of 3-hydroxypropionamidine with acetylacetone was investigated under various conditions. The reaction mixtures, which presumably contained 2-(2-hydroxyethyl)-4,6-dimethylpyrimidine, were difficult to purify. On distillation or under various dehydrating conditions, the product formed a clear viscous tan resin. It seems likely that the desired 2-vinylpyrimidine was actually formed but that the lability toward polymerization, evident in 2-vinylpyridine (2), is accentuated to such an extent that efforts to inhibit it by addition of inhibitors such as hydroquinone and picric acid were unsuccessful.

It was possible to isolate 2-(2-hydroxyethyl)-4-hydroxy-6-methylpyrimidine by condensing I with acetoacetic ester. The lability of the product was indicated by its quantitative conversion to polymer with evolution of just one equivalent of water on refluxing in decalin.



EXPERIMENTAL[3]

3-Hydroxypropionamidine hydrochloride (*I*). Hydrogen chloride (76.7 g., 2.1 moles) was bubbled into a stirred mixture of 142 g. (2.0 moles) of redistilled ethylene cyanohydrin, 64 g. (2.0 moles) of absolute methanol, and 250 ml. of ether, held at 0°. With efficient stirring, the absorption was completed in one hour. The stirrer was raised so that it agitated only the upper ether layer and the mixture was stirred at 0° for three days, during which the lower layer completely solidified. After washing with dry ether, the solid cake was dissolved in 500 ml. of absolute methanol and this solution was poured into a solution of 51 g. (3.1 moles) of ammonia in 500 ml. of methanol maintained at 0°. After stirring the clear solution for one hour, it was evaporated to dryness at about 20 mm. leaving a white residue, 200–225 g. (80–90%). The crude product was purified by dissolving in dry isopropyl alcohol and filtering to remove ammonium chloride, followed by precipitation with three

[3] Combustion analyses by Micro-Tech Laboratories, Skokie, Ill.

volumes of ether. After drying *in vacuo* over phosphorus pentoxide, the hygroscopic white solid melted at 84–85.5°.

Anal. Calc'd for $C_3H_9ClN_2O$: Cl, 28.46. Found: Cl, 28.49 (by titration).

The product was insoluble in benzene, toluene, ether, dioxane, acetone, chloroform, carbon tetrachloride, and petroleum ether. It was readily soluble in water, methanol, and ethanol. It failed to give crystalline salts with picric, picramic, picrolonic, benzoic, tartaric, 3,5-dinitrobenzoic, oxalic, or sulfuric acids. It did not form crystalline complexes with cupric acetate, zinc chloride, mercuric chloride, or auric chloride.

3-Acetoxypropionamidine hydrochloride (*II*). The crude hydroxyamidine (I, 205 g.) was dissolved in 250 ml. of boiling glacial acetic acid and filtered free of undissolved ammonium chloride. The solution was heated to boiling, the flame removed, and 306 g. of acetic anhydride was added in portions so as to maintain boiling. After an hour of refluxing, 250 ml. of acetic acid was removed by distillation at about 40 mm. The cooled residue was added dropwise to 1 liter of acetone. The brown precipitate was dried *in vacuo* over phosphorus pentoxide (m.p. 94–96°) and then recrystallized from absolute ethanol, m.p. 102–103°.

Anal. Calc'd for $C_5H_{11}ClN_2O_2$: C, 36.31; H, 6.66; N, 16.82; Cl, 21.28.
Found: C, 37.10; H, 6.84; N, 16.31; Cl, 21.30.

The *picrate* melted at 171.6–172.0° after four recrystallizations from ethanol.

Anal. Calc'd for $C_{11}H_{13}N_5O_9$: C, 36.77; H, 3.65.
Found: C, 37.44; H, 3.80.

3-Chloropropionitrile was prepared by reaction of thionyl chloride with ethylene cyanohydrin at 50–60° in 60% yield, and by reaction of acrylonitrile and hydrogen chloride without solvent at reflux for twelve hours in 40% yield. The use of ether as a solvent greatly promoted the latter reaction, so that a yield of 80–85% was obtained in three hours at room temperature, b.p. 70–72° (15 mm.). [lit. (3), 65–66.5° (11 mm.)].

Methyl-3-chloropropionimidate hydrochloride (IV). A. *From 3-chloropropionitrile.* Dry hydrogen chloride was passed into a stirred solution of 74 g. (0.82 mole) of 3-chloropropionitrile, 27.2 g. (0.82 mole) of methanol, and 200 ml. of dry ether maintained at 0–5°. Thirty minutes was required to add 30 g. (0.12 mole) of hydrogen chloride. Within two hours at 0°, the reaction mixture had set to a crystalline magma, which was filtered, the product washed with ether, and dried *in vacuo* over phosphorus pentoxide, m.p. 93–94°; yield, 120 g. (93%).

B. *From acrylonitrile.* A total of 219 g. (6.0 moles) of hydrogen chloride was bubbled into 159.2 g. (3.0 moles) of acrylonitrile, 96.0 g. (3.0 moles) of methanol, and 400 ml. of dry ether kept at 0–5°. Crystals began to separate after about six hours but it required two days at 0° for the mixture to solidify. The crystals were collected, washed with ether and dried, m.p. 93–94°; yield, 406 g. (86%).

Anal. Calc'd for $C_4H_8ClNO \cdot HCl$; Ionizable chloride, 22.44; Total chlorine, 44.87.
Found: Ionizable chloride, 23.28; Total chlorine, 44.58 (by titration).

When only 110 g. of hydrogen chloride was added, a 44% yield of the imidate was obtained, m.p. 93–94°.

Hydrolysis to *3-chloropropionamide* was accomplished in aqueous solution at room temperature overnight. The amide was isolated by neutralizing with sodium carbonate and extracting the aqueous solution continuously with ether for ten hours. Evaporation and recrystallization from benzene gave a 65% yield, m.p. 102° [lit. (4), m.p. 102–102.5°].

3-Chloropropionamidine hydrochloride. A. *From methyl 3-chloropropionimidate hydrochloride.* Numerous attempts to effect the conversion of methyl 3-chloropropionimidate hydrochloride to the amidine by treatment with ammonia yielded only ammonium chloride and intractable gummy solids, evidently polymeric.

B. *From 3-hydroxypropionamidine hydrochloride.* During half an hour, 169 g. (1.42 moles) of thionyl chloride was added to a stirred suspension of 93 g. (0.75 mole) of purified hydroxyamidine hydrochloride in 500 ml. of toluene. After standing overnight, the mixture was warmed for half an hour and the toluene was decanted from the dark brown solid. The solid was purified by dissolving in 300 ml. of hot isopropyl alcohol, treating with 10

g. of Norit, filtering, and evaporating. The dark brown hygroscopic solid, 100 g. (93%), melted from 90–95°.

Anal. Calc'd for $C_3H_8Cl_2N_2$: Cl, 49.58. Found: Cl, 48.87.

Condensation of 3-hydroxypropionamidine hydrochloride with acetylacetone. Numerous experiments were carried out in an effort to effect this condensation so that a pure product might be obtained. The method most nearly successful seemed to be the use of sodium methoxide in methanol as a condensing agent.

Sodium methoxide (10.8 g.) was dissolved in 100 ml. of methanol and 20 g. of acetylacetone and 24.5 g. of crude 3-hydroxypropionamidine hydrochloride were added. After refluxing for two hours, the mixture was filtered and the alcoholic solution, which had a strong ammoniacal odor, was immersed in a bath maintained at 50° and the volatile components were removed under 10 mm. pressure. After two days, a yellow, semisolid hygroscopic residue remained which was soluble in water, methanol, ethanol, isopropyl alcohol, Methyl Cellosolve, acetic acid, and pyridine, but completely insoluble in ether, acetone, chloroform, benzene, carbon tetrachloride, and dioxane. Once dissolved, it could be recovered as solid only by evaporation to dryness; attempts to precipitate with a miscible non-solvent always gave two liquid phases. A wide variety of attempts to prepare solid derivatives failed.

Attempted distillation at atmospheric pressure gave a few drops of yellow oil, b.p. 190–210°, and a red, resinous residue, soluble only in water and aqueous acids. Distillation at 0.03 mm. pressure gave about 5 ml. of yellow oil, b.p. 95–100° (0.03 mm.), and 15 g. of polymeric residue. The yellow oil (impure 2-vinyl-4,6-dimethylpyrimidine ?) decolorized permanganate and bromine in carbon tetrachloride, but no crystalline derivative could be obtained and, on attempted redistillation, it resinified.

A similar yellow oil was obtained in better yield by pyrolysis of the crude product over copper turnings at 350°.

Condensation of 3-hydroxypropionamidine hydrochloride with acetoacetic ester. Equivalent quantities of the two reagents (2.0 moles) in 95% ethanol containing (2.0 moles) of sodium methoxide were refluxed for twenty-four hours. The alcoholic filtrate was concentrated to half volume and cooled at 0° for five hours. The yield of white solid was 140 g. (45.6%). Recrystallization from 95% ethanol yielded 110 g. (37%), of 2-(2-hydroxyethyl)-4-hydroxy-6-methylpyrimidine, m.p. 163–165°. Repeated recrystallization from pyridine did not raise the melting point.

Anal. Calc'd for $C_7H_{10}N_2O_2$: C, 54.54; H, 6.54; N, 18.18.
Found: C, 55.88; H, 6.67; N, 18.04.

A 15.4-g. sample (0.1 mole) was dehydrated by refluxing in 150 ml. of decalin containing 1.0 g. of trinitrotoluene. Water was no longer evolved after one hour; exactly 1.8 ml., or just one equivalent, was collected. The decalin solution contained a red resin, insoluble in water, alcohols, and all other common solvents.

Miscellaneous experiments. An attempt was made to condense *2-chlorovinyl methyl ketone* (5) with acetamidine in ethanol. The principal product on attempted distillation was a hard insoluble residue.

An attempt was made to condense *3-ethoxyacrolein diethyl acetal* (6) with acetamidine in ethanol. Some dark brown oil was recovered by extraction but it could not be induced to form a picrate, characteristic of 2-methylpyrimidine (7).

SUMMARY

Of four related nitriles, acrylonitrile, 3-hydroxy-, 3-chloro- and 3-acetoxypropionitriles, only the 3-hydroxy compound could be converted to an amidine by the usual procedure.

3-Hydroxypropionamidine hydrochloride has been successfully converted to the 3-acetoxy and 3-chloro derivatives.

Acrylonitrile, or better 3-chloropropionitrile, have been converted to methyl 3-chloropropionimidate hydrochloride, but attempts to convert this material to the amidine by treatment with ammonia produced only intractable resins.

3-Hydroxypropionamidine hydrochloride has been condensed with acetoacetic ester to give 2-(2-hydroxyethyl)-4-hydroxy-6-methylpyrimidine, which was readily dehydrated to a polymeric resin. Condensation with acetylacetone gave a product, presumably 2-(2-hydroxyethyl)-4,6-dimethylpyrimidine, not satisfactorily characterized but readily converted to polymeric resin.

NOTRE DAME, INDIANA

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(7) GABRIEL, *Ber.*, **37**, 3642 (1904)

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ANTIHISTAMINE AGENTS. III. SUBSTITUTED N,N-DIMETHYL-N′-(2-PYRIDYL)-N′-THENYLETHYLENEDIAMINES AS ANTIHISTAMINE AGENTS

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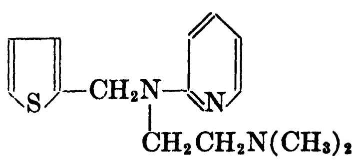
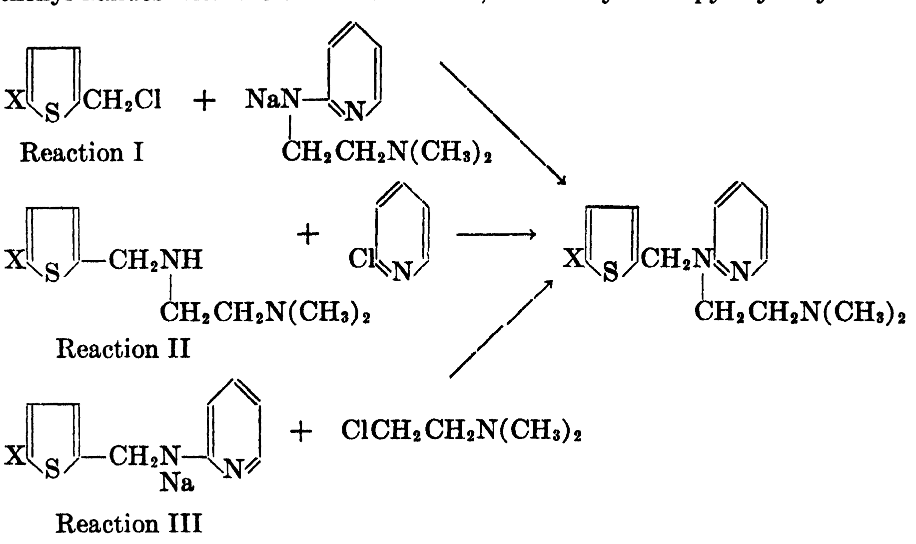
Preliminary announcement of the high antihistamine activity of thenylpyridyldimethylethylenediamines (I) incident to halogenation of the thiophene ring has been made (1). Following this observation, the effects of other substituents in the thiophene and pyridine rings of N,N-dimethyl-N′-2-pyridyl-N′-2-thenylethylenediamine (I) were determined. This paper presents the synthesis of such new compounds and reports their antihistamine activity.



I

The structure assigned to the N,N-dimethyl-N′-2-pyridyl-N′-(5-halo-2-thenyl)ethylenediamines in the earlier report has been confirmed by their synthesis in two other ways. The orientation of the intermediate 5-bromothenyl chloride was shown by its oxidation to 5-bromo-2-thiophenecarboxylic acid. Previously, the compounds had been synthesized by the reaction of the 5-halo-2-thenyl halides with the sodium salt of N,N-dimethyl-N′-2-pyridylethylenedi-



amine (Reaction I). Compounds identical with those prepared from the thenyl halides also resulted from the reaction of 2-chloropyridine with N,N-dimethyl-N′-(5-chloro-2-thenyl)ethylenediamine (Reaction II) and from the reaction of N,N-dimethylaminoethyl chloride and 2-(5-bromo-2-thenyl)aminopyridine (Reaction III).

The new compounds prepared are presented in Table I. They were usually prepared by reaction of a thenyl halide with the sodium or potassium salt of a pyridyldimethylethylenediamine. These salts were conveniently prepared by the reaction of the amine in liquid ammonia or toluene with sodium hydride, or sodium or potassium amide.

The thenyl halides were prepared by three general methods. In the first of these, thiophenes were chloromethylated in an α-position unless both of these were substituted, in which case the chloromethylation occurred in the β-position. Although 2,5-dichlorothiophene was successfully chloromethylated, 2,5-dibromo thiophene failed to react. Attempts to chloromethylate 2-iodothiophene were consistently unsuccessful, decomposition being the invariable result even under the mildest conditions used.

The bromination of various 2-methylthiophenes with N-bromosuccinimide was successful. In the third method, alkyl 2-thienyl carbinols were converted into alkyl 2-thenyl bromides by the action of hydrogen bromide in benzene. Yields were less satisfactory than in the first two methods, possibly because of the ready dehydrobromination of the products, although this assumption has not been proved.

In a large number of cases the instability of the thenyl halides led to their immediate use and they were not analyzed. Their properties and those of the compounds prepared from them were as expected.

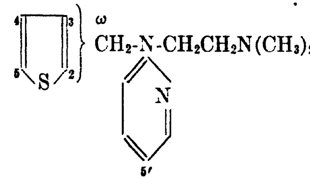
When compound I was treated with bromine, decomposition resulted. However, bromination of compound I having a halogen in the 5-position of the thiophene ring and of N,N-dimethyl-N′-2-pyridylethylenediamine gave compounds brominated in the 5-position of the pyridine ring. These compounds were identified by comparison with those prepared from 2-amino-5-bromopyridine.

Various reactions of the halogen of the N,N-dimethyl-N′-2-pyridyl-N′-(5-halo-2-thenyl)ethylenediamines were tried. In general, reaction with butyllithium, sodium methoxide, or sodium resulted in cleavage of the thenyl group and N,N-dimethyl-N′-2-pyridylethylenediamine resulted. Under other conditions treatment of these compounds with sodium, lithium, methyl lithium, or Grignard reagents resulted in dehalogenation and N,N-dimethyl-N′-2-pyridyl-N′-2-thenylethylenediamine was produced. In all of the above reactions the bromo compounds proved to be more reactive than the chloro. Evidence for metallation was obtained only in the case of the action of butyllithium on the bromo compound followed by carbonation to give a low yield of the corresponding 5-carboxy compound.

When the compounds of this series were tested *in vitro* against histamine (see Table I) none was as active as either N,N-dimethyl-N′-2-pyridyl-N′-(5-bromo-2-thenyl)ethylenediamine or its chloro analog.

TABLE I

N,N-DIMETHYL-N′-2-PYRIDYL-N′-THENYLETHYLENEDIAMINES



CPD.	—CH_2—	2 OR 3	5	ω	5′	METHOD[l] OF Prep'n	Work-up	B.P. °C/MM.	CRYSTAL SOLVENT	M.P. °C[j]	SALT	YIELD %	EMP. FORMULA ANALYTICAL FORM	CALC'D % C	% H	% N	Eq. Wt.	FOUND % C	% H	% N	Eq. Wt.	H Ratio[k]
1	2							123–135 / 0.1		162–165	A											1–10
2	2		Cl			II		155–156 / 1		106–108	A		$C_{14}H_{19}Cl_2N_3S$	50.6	5.8	12.6		50.9	6.1	12.3		10–100
3	2		Cl							105–106	B		$C_{14}H_{21}ClN_3O_4PS$			10.7				10.5[e]		10–100
4	2		Cl							115–118	C		$C_{20}H_{26}ClN_3O_7S$			8.6				8.5[e]		10–100
5	2		Br			III	2	173–175 / 1	Ethyl acetate	124–126	A	<19	$C_{14}H_{19}BrClN_3S$[a]	44.6	5.1	11.1		44.9	5.2	11.0		10–100
6	2	3-Br	Br			I-KNH_2	1	150–160 / 0.001	Abs. alc.	208–209	A	39	$C_{14}H_{18}Br_2ClN_3S$[b]			9.2				9.1		0.01–0.1
7	2		*t*-Bu			I-$NaNH_2$	4	185–190 / 3.5	Toluene	145–146	A	10	$C_{18}H_{28}ClN_3S$	61.1	8.0	11.9		61.2	7.8	11.7		0.01–0.1
8	3	2-Cl	Cl			I-$NaNH_2$	3	174–180 / 1	Ethyl acetate or benzene	168–170	A	25	$C_{14}H_{18}Cl_3N_3S$[c]			11.5				11.7		0.1–1.0
9	2				Br	I-KNH_2	1	175–185 / 0.6	Methyl ethyl ketone	140–141	A	11	$C_{14}H_{19}BrClN_3S$	44.6	5.1	11.2		44.6	5.4	11.3		0.1–1.0
10	2	3-Br				I-$NaNH_2$	2		Benzene	184–185	A	55	$C_{14}H_{19}BrClN_3S$[f]			11.2				10.9		0.1–1.0
11	2		Cl		Br	I-$NaNH_2$	5		Ethyl acetate or Methyl ethyl ketone	136–137	A	48	$C_{14}H_{18}BrCl_2N_3S$	40.8		10.2	411	41.0[g]		10.2	410	0.1–1.0

12	2		*t*-Bu		Br	I-NaH	5		Methyl ethyl ketone	175–176	A	<1	$C_{18}H_{27}BrClN_3S$[h]	49.9		9.7	433	49.8[g]		9.6	431	0.01–0.1
13	2		Br		Br	I-NaH	2	175–190/0.0001	"	163–166	A	15	$C_{14}H_{18}Br_2ClN_3S$	36.9	4.0	9.2		37.1	4.3	8.9		0.01–0.1
14	2			*n*-C_3H_7		I-NaH	2	130–135/0.5				5	$C_{17}H_{25}N_3S$	67.3	8.3	13.9		67.4	7.4	13.5		0.1–1.0
15	2			CH_3		I-$NaNH_2$	2	150–151/1	*i*-Propanol	172–173	A	23	$C_{15}H_{22}ClN_3S$[i]	57.9	7.7	13.5	311.5	58.1	7.4	13.2	307.5	0.1–1.0
16	2		COOH							198–200	D	5	$C_{27}H_{25}N_9O_{16}S$[d]	42.5	3.3	16.5		42.6	3.4	16.5		0.01–0.1

A. hydrochloride.
B. dihydrogen phosphate.
C. dihydrogen citrate.
D. dipicrate.

[a] S, Calc'd 8.5; found, 8.7.
[b] Cl^-, Calc'd 7.8; found (Volhard) 7.7.
[c] Cl^-, Calc'd 9.7; found (Volhard) 9.6.
[d] Picric acid, Calc'd 60.1%; found (spectrally) 58.6.
[e] Macro Kjeldahl.
[f] Cl^-, Calc'd 7.4; found 7.5.
[g] van Slyke wet carbon.
[h] S, Calc'd 7.4; found 7.5.
[i] Cl^-, Calc'd 11.4; found (Volhard) 11.3.
[j] Melting points were taken either in a bath or on a Fisher-Johns block.
[k] H ratio = μ g. histamine (to produce a given contraction)/μ g. compound (required to suppress this response), and was determined on the isolated guinea pig gut by the method of (14).
[l] For examples of the various methods, see Experimental.

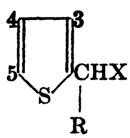
EXPERIMENTAL[1]

The thenyl halides used are described in Table II.

Method I. Workup 1. N,N-Dimethyl-N′-2-pyridyl-N′-(3,5-dibromo-2-thenyl)ethylenediamine. Thirty and eight-tenths grams (0.092 mole) of 3,5-dibromo-2-thenyl bromide was condensed with 15.5 g. (0.095 mole) of N,N-dimethyl-N′-2-pyridylethylenediamine (3) by the usual process using potassium amide in toluene. After filtration, the toluene was extracted with dilute hydrochloric acid and the acid solution made strongly basic by the addition of solid sodium hydroxide. The oil which separated was extracted with benzene. The benzene was distilled and the residue was vaporized at very low pressure in a short-path still. A forerun was collected at a bath temperature of 110–120° and a pressure

TABLE II

THENYL HALIDES



X	R	3	4	5	METHOD OF PREP'N	YIELD, %	PAPER REFS. INTERMEDIATE	B.P., °C./MM.
Br	H	Br	H	Br	A	61	(2)	104–108/1
Br	H	Br	H	H	A	86	(2)	60–125/1[c]
Cl[a]	H	Cl	H	Cl	B	10	Texaco	125–128/30
Cl	H	H	H	*t*-Bu	B	52	Socony-Vacuum	67–71/1
Br	CH_3	H	H	H	C	20	C	
Br	*n*-C_3H_7	H	H	H	C	24	C	63/3
2,5-Dichloro-3-thenylchloride[b]					B	11	Texaco	125–128/30

Methods of preparation:

A. N-Bromosuccinimide on methyl compound.

B. Chloromethylation of 2-H thiophene by method of (1).

C. see Experimental.

[a] Hydrolysable Cl^-, Calc'd: 7.6; Found: 7.3, n_D^{20} 1.5258.

[b] Hydrolysable Cl^-, Calc'd: 17.6; Found: 17.3, n_D^{25} 1.5805.

[c] Superheat.

of about 0.01 mm. This was followed by a fraction at a bath temperature of 150–160° and a pressure of 0.001 mm.; yield, 15 g. This was converted into its monohydrochloride by treatment with the theoretical amount of alcoholic hydrogen chloride. The solid was purified by recrystallization from absolute alcohol.

Method I. Workup 2. N,N-Dimethyl-N′-2-pyridyl-N′-(3-bromo-2-thenyl)ethylenediamine hydrochloride. Twenty and five-tenths grams of N,N-dimethyl-N′-2-pyridylethylenediamine was converted to its sodium salt in liquid ammonia by treatment with sodamide freshly prepared from 2.9 g. (0.126 atom) of sodium. The ammonia was displaced by 150 cc. of dry toluene and 31.8 g. (0.124 mole) of 3-bromo-2-thenyl bromide was added. The reaction was stirred and heated on the steam-bath for two hours. After standing at room temperature overnight, the reaction mixture was filtered and the toluene was distilled at

[1] All melting points are corrected. Combustion analyses were carried out in these Laboratories under the direction of Dr. J. A. Kuck. In all cases the figures presented are the average of two values not differing by more than 0.3.

reduced pressure. The residue was fractionated at about 1 mm. The forerun boiling at 50–144° was discarded; the remainder distilled at 148–153°, and weighed 24.6 g. This was redistilled to give 23 g.; n_D^{25} 1.5988; b.p. 170–180° (*ca.* 1 mm.), although this represents considerable superheating. On treating the material with an equivalent of alcoholic hydrochloric acid the salt precipitated. Crystallization from benzene containing a small proportion of alcohol does not improve the melting point.

Method I. Workup 3. N,N-Dimethyl-N′-2-pyridyl-N′-(2,5-dichloro-3-thenyl)ethylenediamine. Nine and two-tenths grams of 2,5-dichloro-3-thenyl chloride reacted with the sodium salt of N,N-dimethyl-N′-2-pyridylethylenediamine prepared from 7.8 g. (0.047 mole) of the amine and the sodamide from 1.06 g. (0.046 mole) of sodium in liquid ammonia. The reaction was carried out in 250 cc. of toluene which had displaced the ammonia in which the sodium salt was formed. After heating for four hours on the steam-bath, the mixture was allowed to stand overnight and then hydrolyzed and filtered. The toluene layer was separated, dried over sodium sulfate, and the toluene distilled. The concentrate was extracted with 50 cc. of anhydrous ether and the ether-soluble material fractionated to give 3.86 g. of product boiling at 174–180° (1 mm.), n_D^{25} 1.5866. The material was converted to its monohydrochloride by treatment with an equivalent of absolute alcoholic hydrogen chloride and precipitation with ether. Two and three-tenths grams of a white solid melting at 158–163° was obtained. After crystallization from ethyl acetate and alcohol, followed by benzene, 1.28 g. of white plates was obtained.

Method I. Workup 4. N,N-Dimethyl-N′-2-pyridyl-N′-(5-t-butyl-2-thenyl)ethylenediamine hydrochloride. Sodamide from 4.6 g. (0.2 mole) of sodium was treated with 33 g. (0.2 mole) of N,N-dimethyl-N′-2-pyridylethylenediamine in toluene and this product in 500 cc. of toluene was treated with 37.3 g (0.2 mole) of 5-*t*-butyl-2-thenyl chloride at room temperature with cooling. After stirring for two hours at room temperature, 300 cc. of water was added cautiously, and the layers were separated. The toluene layer was dried over potassium carbonate and the toluene was distilled at about 30 mm. pressure. The residue was fractionated at 3.5 mm. pressure. A forerun of 7.5 g. boiling at 70–78° was discarded and 7.7 g. of a fraction of b.p. 185–190° was obtained. The material was converted to its monohydrochloride by treatment with an equivalent of alcoholic hydrogen chloride and precipitation with ether. The crystals were hygroscopic and the hydrochloride was reconverted to the free base by solution in water, treatment with sodium hydroxide, and extraction with ether. The ether was distilled and the residue was again treated with an equivalent of alcoholic hydrogen chloride. The crystals obtained in this fashion were nonhygroscopic and were crystallized from toluene four times to a constant m.p. of 145–146°, using Norit the first two times.

1-(2-Thienyl)ethanol [for another method of preparation see (4)] was prepared by the addition of 0.56 mole of 2-thiophenaldehyde (Arapahoe) to a Grignard reagent prepared from 0.75 mole of methyl iodide and 0.5 g. of magnesium in ether. The reaction mixture was stirred for ten minutes after the addition of the aldehyde was complete and then poured onto cracked ice. After the addition of sulfuric acid, the ether layer was separated and the aqueous layer extracted six times with ether. The ether layers were combined, dried, and the ether distilled. The product was obtained in 79.4% yield, b.p. 89–92° (11 mm.).

1-(2-Thienyl)ethyl bromide. A solution of 30 g. of the carbinol and 150 cc. of benzene was slowly saturated with anhydrous hydrogen bromide and then treated with hydrogen bromide for forty minutes longer (5). The solution was dried over sodium sulfate, the benzene was distilled, and the residue fractionated. The product was unstable even in the refrigerator.

1-(2-Thienyl)butanol was prepared in 84.1% yield by the addition of 0.7 mole of 2-thiophenaldehyde to a Grignard reagent prepared from 1 mole of propyl bromide and 1 mole of magnesium in ether (dried with calcium hydride). The product weighed 90 g. and boiled at 84–86° (3 mm.).

1-(2-Thienyl)butyl bromide. The 90 g. (0.58 mole) of 1-(2-thienyl)butanol was treated with anhydrous hydrogen bromide in 400 cc. of benzene. An orange water layer separated

as the reaction proceeded and the reaction was stopped after two hours. The benzene was washed with sodium bisulfite solution, evaporated, and the black residue was fractionally distilled.

N,N-Dimethyl-N'-(5-bromo-2-pyridyl)ethylenediamine dihydrochloride. A. *From N,N-dimethyl-N'-2-pyridylethylenediamine.* One hundred grams (0.61 mole) of this compound in 500 cc. of chloroform was cooled in an ice-bath and treated with 105 g. (0.65 mole) of bromine in thirty minutes. The chloroform was then extracted with several 150-cc. portions of water and these extracts combined. The aqueous solution was made strongly alkaline and extracted with ether to remove the separated oil. The ether was distilled and the product was fractionated at 0.1 mm. pressure; 89 g. (60%) was collected at 102–106°, n_D^{30} 1.5745. A sample of this was converted to the dihydrochloride by treatment with alcoholic hydrogen chloride and recrystallized from 95% alcohol. The melting point was 224–227° (dec.) and was not depressed by mixture with the material prepared by Method B. When carried out in aqueous solution the bromination gave a 76% yield. Some dibromo product was formed, however, which complicated the purification.

B. *From 2-amino-5-bromopyridine.* The potassium salt of 86 g. (0.5 mole) of 2-amino-5-bromopyridine (6) was made in liquid ammonia from freshly prepared potassium amide. After stirring for one-half hour the ammonia was replaced by toluene and 53.8 g. (0.5 mole) of dimethylaminoethyl chloride (7) was added. The reaction mixture was heated with stirring on a steam-bath for eighteen hours, cooled, and filtered. The filtrate was concentrated by distillation and the residue was distilled *in vacuo*. The fraction of b.p. 120–130° (1 mm.) weighed 51 g. (42%). This was converted into its dihydrochloride by treatment with alcoholic hydrogen chloride; 60 g. of material of m.p. 175–190° was obtained. After two recrystallizations from 95% alcohol the colorless material melted at 226–228° with decomposition.

Anal. Calc'd for $C_9H_{16}BrCl_2N_3$: N, 13.3. Found: N, 13.0, 13.1.

N,N-Dimethyl-N'-(5-bromo-2-pyridyl)-N'-(5-chloro-2-thenyl)ethylenediamine monohydrochloride. The material was prepared more satisfactorily than is shown in the Table by the treatment of a solution of 7.5 g. (0.023 mole) of N,N-dimethyl-N'-2-pyridyl-N'-(5-chloro-2-thenyl)ethylenediamine monohydrochloride (1) in 50 cc. of chloroform with a solution of 4 g. (0.025 mole) of bromine in 25 cc. of chloroform at room temperature over a forty-five minute period. At the end of the addition the reaction mixture was extracted with 50–75 cc. of a 2% sodium hydroxide solution and the chloroform layer was separated and concentrated. The dark residue was dissolved in dilute hydrochloric acid and decolorized with Darco. The solution was made alkaline and the separated oil extracted with ether. Concentration of the ether gave 6.1 g. (65%) of light red oil. After treatment with an equivalent of alcoholic hydrogen chloride the monohydrochloride was precipitated by ether; yield, 4.3 g. (45%), melting at 127–129°. When mixed with material prepared by Method A, the melting point was not depressed.

N,N-Dimethyl-N'-(5-bromo-2-pyridyl)-N'-(5-bromo-2-thenyl)ethylenediamine monohydrochloride. The material was obtained more satisfactorily than is shown in the Table by the bromination at room temperature of 1.0 g. (0.003 mole) of N,N-dimethyl-N'-2-pyridyl-N'-(5-bromo-2-thenyl)ethylenediamine monohydrochloride (1) in 25 cc. of chloroform, with a solution of 0.43 g. (0.0027 mole) of bromine in 20 cc. of chloroform. The chloroform solution was extracted with 100 cc. of water containing 1 cc. of concentrated hydrochloric acid. The product thus extracted could not be converted to a suitable derivative. The chloroform solution was treated with anhydrous potassium carbonate and concentrated to give 0.9 g. of a light red oil. This was converted to a monohydrochloride by treatment with one equivalent of alcoholic hydrogen chloride. After three crystallizations from 10-cc. portions of methyl ethyl ketone, 0.35 g. of product melting constantly at 164–164.5° was obtained. This melting point was not depressed by the material prepared by Method A.

An attempt to brominate N,N-dimethyl-N'-2-pyridyl-N'-2-thenylethylenediamine gave only intractable tars in addition to more than a 50% recovery of the starting material in an impure form.

2-(5-Chloro-2-thenyl)aminopyridine. One mole of the sodium salt of 2-aminopyridine was prepared by adding 94 g. (1.0 mole) of 2-aminopyridine to 24 g. (1.0 mole) of sodium hydride (du Pont) in 400 cc. of dry toluene in forty-five minutes and heating on a steam-bath for one and three-quarter hours. After cooling the mixture to room temperature, 83.5 g. (0.5 mole) of 5-chloro-2-thenyl chloride was added dropwise with ice cooling. The mixture was then heated on the steam-bath for four hours and hydrolyzed by the addition of 30 cc. of alcohol, then 300 cc. of water. After standing overnight, the black toluene layer was separated and the aqueous portion extracted with three 500-cc. portions of ether and the extracts combined with the toluene. Following drying over sodium carbonate and distillation of solvents, the product was fractionated at 1 mm. to yield 10 g. of aminopyridine, 36 g. of material boiling at 170–192°, and 53 g. of residual tar. The 36 g. of distillate solidified and was recrystallized from methyl ethyl ketone to give 23 g. of the desired product (20% yield), m.p 71–74°. A further crystallization from this solvent gave 17 g., m.p. 84–86°.

A 1-g. sample was converted to the hydrochloride by treatment with an equivalent of alcoholic hydrogen chloride and precipitation of the product with ether; m.p. 110–115°, neutral equivalent 275 (theoretical 261). Recrystallization from methyl ethyl ketone raised the m.p. to 125–127°.

Anal. Calc'd for $C_{10}H_{10}Cl_2N_2S\cdot$ N, 10.7. Found: N, 10.6.

2-(5-Bromo-2-thenyl)aminopyridine. One mole of the sodium salt of 2-aminopyridine and 0.75 mole of 5-bromo-2-thenyl chloride were reacted as above. Twenty-five grams of 2-aminopyridine (27%) was recovered at 89–150° (9 mm.). Fractional distillation of the residue at 1 mm. gave 66 g. of material boiling at 145–170°, 28 g. boiling at 170–202°, and 70.4 g. of dark residue The first fraction was crystallized from about 300 cc. of heptane to give 53 g. of product of m p. 80–82°. The second fraction was extracted with 100 cc. of hot heptane and yielded, in two extractions, 16.8 g., m.p. 74–80°. This was recrystallized from 150 cc. of heptane to give 15.6 g. of material melting at 81–83°. The total yield of pure material was 68 6 g. (33%). The material was converted to its hydrochloride by treatment with an equivalent of alcoholic hydrogen chloride followed by precipitation by ether. After crystallization from isopropanol it melted at 151–153.5°.

Anal. Calc'd for $C_{10}H_9BrN_2S\cdot HCl$; N, 9.2; Neutral equivalent, 305.6.

Found· N, 9.2; Neutral equivalent, 313.

Method III. N,N-Dimethyl-N'-2-pyridyl-N'-(5-bromo-2-thenyl)ethylenediamine. Five and four-tenths grams (0.02 mole) of 2-(5-bromo-2-thenyl)aminopyridine was added to a suspension of sodamide which had been freshly prepared from 0.69 g. (0.03 mole) of sodium in 200 cc. of liquid ammonia. The mixture was stirred for five minutes and 3.22 g. (0.03 mole) of β-dimethylaminoethyl chloride (7) was added. Dry toluene (100 cc.) was added and the mixture was heated three hours at 90° with stirring. It was cooled, 20 cc. of water was added, the toluene layer was separated and the aqueous layer was extracted with two 20-cc. portions of toluene. The toluene was distilled in vacuum and the residue was fractionated at about 1 mm. The fraction boiling at 170–187° was treated with an equivalent of alcoholic hydrogen chloride and the hydrochloride was precipitated with ether. This was recrystallized from ethyl acetate to give a low yield (the crude yield was 19%) of N,N-dimethyl-N'-2-pyridyl-N'-(5-bromo-2-thenyl)ethylenediamine hydrochloride, m.p. 126–129°. The m.p. was not depressed by material prepared in another way (1).

N,N-Dimethyl-N'-2-pyridyl-N'-(5-bromo-2-thenyl)propylenediamine. 1-Dimethyla-mino-2-propanol (8) was converted into 2-chloro-N,N-dimethylpropylamine hydrochloride in 32% yield by reaction with thionyl chloride; this was converted to the free base in 63% yield immediately prior to use.

The potassium salt of 2-(5-bromo-2-thenyl)aminopyridine was prepared by adding 26.9 g. (0.10 mole) of the amine to potassamide (0.10 mole) in liquid ammonia. After fifteen minutes, 13.5 g. (0.11 mole) of the above chloride was added, stirred five minutes, and then 150 cc. of dry toluene was added. The reaction was carried out and worked up as in the preceding example. The toluene was concentrated by distillation on the steam-bath at water-

pump pressure and the residue was distilled at about 0.1 mm. to give a forerun of 5 g. of material boiling at 140–164° (discarded), and 18.8 g. boiling at 164–175°. The latter was refractionated, yielding 12 g. at 135–164° and 5 g. at 164–168°. The first fraction was partially unreacted 2-(5-bromo-2-thenyl)aminopyridine which crystallized out on treatment with petroleum ether. The residual oil from evaporation of the petroleum ether gave an oily hydrochloride, as did the second fraction. These were combined, reconverted to the base, and redistilled to give a main fraction boiling at 170–174° (0.5–1 mm.). No satisfactory salt was obtained from samples of this.

Anal. Calc'd for $C_{15}H_{20}BrN_3S$: C, 50.8; H, 5.7; N, 11.9.
Found: C, 51.1; H, 5.5; N, 11.3.

No attempt was made to prove whether the product was one of the isomers, $R_1R_2NCH_2\underset{\underset{CH_3}{|}}{C}HN(CH_3)_2$ or $R_1R_2N\underset{\underset{CH_3}{|}}{C}HCH_2N(CH_3)_2$, or a mixture of the two. The last possibility might be expected, since it has been shown that 2-chloro-N,N-dimethylpropylamine gives analogous isomers in the preparation of Amidone (9).

N,N-Dimethyl-N'-(5-chloro-2-thenyl)ethylenediamine. During thirty minutes 133.6 g. (0.80 mole) of 5-chloro-2-thenyl chloride (1) was added with stirring to 282 g. (3.2 moles) of N,N-dimethylethylenediamine while cooling in an ice-bath. The temperature of the reaction mixture slowly rose to 70° and the mixture was stirred for thirty minutes without heating and was then heated on a steam-bath for two hours. The cooled mixture was treated with aqueous alkali and extracted with five portions of ether. The extract was dried with sodium sulfate, the ether distilled, and the residue distilled in vacuum. Some unreacted diamine was collected in the forerun and discarded. The product, b.p. 105–107° (2 mm.), n_D^{28} 1.5250, weighed 93 g. (53%). The material was converted to a hydrochloride by solution in alcoholic hydrochloric acid and precipitation with ether. After three crystallizations from aqueous alcohol it melted at 199–201° with some sintering at 189°.

Anal. Calc'd for $C_9H_{15}ClN_2S \cdot 2HCl \cdot 1/2\ H_2O$: C, 36.0; H, 6.0; N, 9.3.
Found: C, 36.0; H, 6.5; N, 9.1.

Method II. N,N-Dimethyl-N'-2-pyridyl-N'-(5-chloro-2-thenyl)ethylenediamine. A solution of 20.7 g. (0.095 mole) of N,N-dimethyl-N'-(5-chloro-2-thenyl)ethylenediamine and 21.4 g. (0.189 mole) of 2-chloropyridine in 15.0 cc. of 2,6-lutidine was refluxed for forty-eight hours. At twenty-four hours a Volhard titration (10) of an aliquot showed the formation of 11% of the theoretical chloride ion. The mixture was diluted with aqueous alkali and extracted five times with ether. The ether extract was dried over sodium sulfate and concentrated. The residue was distilled in a vacuum and the lower-boiling fraction discarded. Three fractions were collected: (a) b.p. 115–162° (0.6 mm.); (b) 162–165° (0.6 mm.); (c) 165–167° (0.6 mm.). Fraction 2 had n_D^{29} 1.5812 and weighed 4.95 g. It was dissolved in an equivalent amount of alcoholic hydrochloric acid and the product precipitated with ether. The gummy precipitate was dissolved in water, basified, and the base extracted with ether. The ether solution was dried, concentrated, and the residue distilled in a vacuum. Two fractions were collected: 127–152° (0.3 mm.), n_D^{25} 1.565, and 148–153° (0.3 mm.), n_D^{25} 1.585; weight, 2.8 g. The second fraction was again converted to a salt with hydrogen chloride and ether. Crystals and a gum separated. The crystals were collected and crystallized from benzene, m.p. 105–107°. They did not depress the m.p. of a sample of the compound prepared in a different manner (1). The non-crystalline gum gave a picrate identical with that from N,N-dimethyl-N'-2-pyridyl-N'-(5-chloro-2-thenyl)ethylenediamine. This picrate is best prepared in and recrystallized from glacial acetic acid; m.p. 145–148°.

Anal. Calc'd for $C_{14}H_{18}ClN_3S \cdot 2C_6H_3N_3O_7$: N, 16.7. Found: N, 16.7.

N,N-Dimethyl-N'-(5-bromo-2-thenyl)ethylenediamine. A solution of 17.6 g. (0.20 mole) of N,N-dimethylethylenediamine in 25 cc. of benzene was refluxed with stirring and a solution of 21.1 g. (0.10 mole) of 5-bromo-2-thenyl chloride in 25 cc. of benzene added dropwise in the course of forty-five minutes. A white crystalline precipitate formed. The reaction mixture was refluxed for an additional four hours, cooled, and worked up as for the chloro compound. The product, b.p. 93–96° (0.2–0.3 mm.), n_D^{29} 1.5395, weighed 7.47 g.

For analytical purposes, 0.47 g. of the product was treated with 2.5 cc. of 1.59 *N* alcoholic hydrochloric acid. The resultant white precipitate was dissolved by the addition of 25 cc. of boiling absolute ethanol, the minimum amount required for complete solution. After cooling, 0.42 g. of the hydrochloride, m.p. 191–217° (d) was obtained. After two recrystallizations from absolute alcohol, the dihydrochloride melted at 189–220° (d).

Anal. Calc'd for $C_9H_{15}BrN_2S \cdot 2HCl$: N, 8.3. Found: N, 8.2.

5-Bromo-2-thiophenecarboxylic acid from 5-bromo-2-thenyl chloride. To a solution of 17.5 g. of potassium permanganate and 26 g. of sodium hydroxide in 700 cc. of water was added 12.7 g. of 5-bromo-2-thenyl chloride (1), and the mixture was stirred at room temperature for sixteen hours. Sodium bisulfite was added until the green color had been destroyed. After the mixture had been filtered, the oil was removed by extraction with ether, and acidification of the aqueous solution gave 0.65 g. of white needles, m.p. 139–141°. The ethereal solution was concentrated, and the resulting oil was stirred with a solution of 17.5 g. of potassium permanganate and 26 g. of sodium hydroxide in 700 cc. of water for an additional forty-four hours at room temperature. Filtration and acidification yielded 2.1 g. of the acid, m.p. 139–141°. Concentration of the filtrate afforded an additional 0.34 g., m.p. 138–140° (total yield, 3.09 g.; 25%). This material did not depress the melting point of 5-bromo-2-thiophenecarboxylic acid prepared from thiophene-2-carboxylic acid (11) and had an identical infrared spectrum.[2]

N,N-Dimethyl-N'-2-pyridyl-N'-(5-carboxy-2-thenyl)ethylenediamine dipicrate. A solution of 14.5 g. (0.042 mole) of N,N-dimethyl-N'-2-pyridyl-N'-(5-bromo-2-thenyl)ethylenediamine in 50 cc. of ether was added rapidly to a solution of 0.05 mole of butyllithium and 35 cc. of ether (12) with vigorous stirring. The reaction mixture was maintained at −35° for fifteen minutes. Solid, ground, carbon dioxide was then added in large excess and the reaction mixture was stirred for forty minutes. At the end of this time the mixture was hydrolyzed with 75–100 cc. of water and filtered to remove lithium carbonate and break the emulsion. The ether layer was extracted with 75 cc. of dilute sodium hydroxide in two portions. These were combined, acidified with acetic acid, and concentrated to leave a viscous tar. The tar was dissolved in alcohol, filtered, and diluted with several volumes of ether to precipitate a brown solid. The brown solid was dissolved in alcohol and treated with an alcoholic solution of 7 g. of citric acid, which precipitated a sodium or lithium salt of citric acid. The alcohol filtrate was dissolved in dilute sodium hydroxide and extracted with ether. The solution was then acidified with hydrochloric acid and extracted with ether, the extracts discarded, and the aqueous solution concentrated to an oily solid mixture on the steam-bath. This was extracted with alcohol to leave an insoluble inorganic solid and give 5.7 g. of a light red oil, insoluble in ether but soluble in water. An attempt to form a hydrochloride of this material gave only hygroscopic solids which were combined, dissolved in water, neutralized with ammonia, evaporated to dryness, and dissolved in alcohol. The alcoholic solution was treated with an equal volume of 50 cc. of saturated alcoholic picric acid and cooled to precipitate a picrate. After two crystallizations from 300-cc. portions of absolute alcohol the picrate was obtained as yellow needles melting constantly at 198–200°, yield 1.45 g.

Anal. Calc'd picric acid, 60.1%. Found: 58.6%. This was found by ultraviolet spectral determination. For other analyses see the table.

In addition to this material, there was obtained from the original ether layer of the reaction some of the debrominated compound which was identified by distillation, conversion to its monohydrochloride and comparison with an authentic sample.

Reactions of N,N-dimethyl-N'-2-pyridyl-N'-(5-bromo-2-thenyl)ethylenediamine.

1. When the compound and sodium methoxide were heated in methanol in a bomb tube at 150° for six hours and the basic product was fractionated, a 21% recovery of the starting material and a 28% yield of N,N-dimethyl-N'-2-pyridylethylenediamine was obtained.

2. When the bromo compound was treated with sodium sand and propyl iodide, both

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[2] We are indebted to Dr. R. C. Gore of the Physics Division of these Laboratories for this measurement.

N,N-dimethyl-N′-2-pyridyl-N′-2-thenylethylenediamine and N,N-dimethyl-N′-2-pyridylethylenediamine were isolated.

3. When the bromo compound was treated with sodium sand in hot benzene for twenty-four hours, a 20–30% yield of the debrominated compound was obtained. When the corresponding chloro compound was used, however, the starting material was recovered unchanged.

4. When the bromo compound was treated with finely divided lithium, both the debrominated compound and N,N-dimethyl-N′-2-pyridylethylenediamine were recovered. If lithium sand was used, an increased reaction rate resulted and none of the debrominated compound was recovered. The compound was also debrominated by the action of propyllithium. No alkylated product was isolated; *cf.* (13).

N,N-Dimethyl-N′-2-pyridyl-N′-(5-chloro-2-thenyl)ethylenediamine dihydrogen phosphate. Three grams (0.01 mole) of the base (1) was dissolved in 10 cc. of absolute alcohol containing 1.16 g. (0.01 mole) of 85% phosphoric acid. The salt was precipitated by the addition of ether (crystallization could be induced directly with the aid of seeds) and solidified by trituration with acetone. After crystallization from alcohol it melted at 105–106°. The compound was not as hygroscopic as the hydrochloride but was markedly more so than the dihydrogen citrate.

Attempts to make the monohydrogen and neutral phosphates by the same method led only to the dihydrogen phosphate.

N,N-Dimethyl-N′-2-pyridyl-N′-(5-chloro-2-thenyl)ethylenediamine dihydrogen citrate. A solution of 118 g. (0.398 mole) of the base and 83.5 g. (0.397 mole) of citric acid hydrate in 425 cc. of warm absolute alcohol was crystallized by the addition of seeds obtained from a smaller preparation by precipitation with ether. The yield was 174.6 g. (90%); m.p. 102–106°. Crystallization from 500 cc. of absolute alcohol gave 156 g. melting at 115–118°, and this was not changed by further crystallization.

Attempts to prepare the monohydrogen and neutral citrates led only to the dihydrogen citrate. The dihydrogen citrate is non-hygroscopic, gaining less than 0.5% in weight when exposed in a closed vessel to an atmosphere saturated with water vapor for twenty-four hours.

N,N-Dimethyl-N′-2-pyridyl-N′-(5-chloro-2-thenyl)ethylenediamine methiodide. Ten grams (0.034 mole) of N,N-dimethyl-N′-2-pyridyl-N′-(5-chloro-2-thenyl)ethylenediamine was dissolved in ether and treated with 4.78 g. (0.034 mole) of methyl iodide. Crystals formed quickly and were filtered off after twenty-four hours. These (12.96 g., 88%) were crystallized from 50 cc. of water and from 150 cc. of acetone to give material of m.p. 159–160° (unchanged from the water crystallization).

Anal. Calc'd for $C_{15}H_{21}ClIN_3S$; N, 9.6. Found: N, 9.7.

N,N-Dimethyl-N′-2-pyridyl-N′-(5-chloro-2-thenyl)ethylenediamine benzochloride. The above preparation was repeated using 4.26 g. of benzyl chloride in place of the methyl iodide. It was necessary to reflux the solution to cause the reaction to take place and the ether was finally displaced with benzene to complete the reaction. The gummy precipitate was washed with acetone and crystallized from the same solvent, using Darco. Material of m.p. 94–96° was obtained. The m.p. was not raised by further recrystallization.

Anal. Calc'd for $C_{21}H_{25}Cl_2N_3S$; N, 10.0. Found: N, 10.2.

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We are indebted to Dr. J. T. Litchfield, Jr., Mrs. M. A. Peluso, Miss L. Alonso and Miss M. Jaeger for the antihistamine results which are reported in the table.

SUMMARY

Twelve new thenylated N,N-dimethyl-N′-pyridylethylenediamines have been prepared.

The structure of some previously prepared compounds of this class has been proved.

The *in vitro* antihistamine activities of these compounds have been reported.

STAMFORD, CONN.

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[Contribution from the Chemotherapy Division of the Stamford Research Laboratories, American Cyanamid Company, and the Research Department of the Calco Chemical Division, American Cyanamid Company]

ANTIHISTAMINE AGENTS. IV. HALOGENATED N,N-DIMETHYL-N'-BENZYL-N'-(2-PYRIDYL)-ETHYLENEDIAMINES

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The introduction of halogen into the thiophene group of N,N-dimethyl-N'-(2-pyridyl)-N'-(2-thenyl)ethylenediamine has been effective in some instances in enhancing the antihistamine activity of that compound (1, 2). Also, high antihistamine activity has been reported for N,N-dimethyl-N'-(4-methoxybenzyl)-N'-(2-pyridyl)ethylenediamine (Neoantergan) (3, 4) as well as for the parent compound, N,N-dimethyl-N'-benzyl-N'-(2-pyridyl)ethylenediamine (Pyribenzamine) (4). In view of these results, it seemed of interest to determine the effect of halogenation on the antihistamine activity of N,N-dimethyl-N'-benzyl-N'-(2-pyridyl)ethylenediamine. The compounds prepared are listed in Table I along with their relative antihistamine activities.

Compounds I to VI were prepared by the condensation of N,N-dimethyl-N'-(2-pyridyl)ethylenediamine (DPE) with the appropriate halogenated benzyl halide in the presence of alkali amide or hydride. The yields in general were about 40–60%. In most cases no further attempt was made to improve these yields, since the primary object was to obtain sufficient material for preliminary pharmacological testing.

Direct bromination of N,N-dimethyl-N'-benzyl-N'-(2-pyridyl)ethylenediamine resulted in substitution in the 5-position of the pyridine ring to yield N,N-dimethyl-N'-benzyl-N'-(5-bromo-2-pyridyl)ethylenediamine (VIII). The orientation of the substituent was proved by the alternate synthesis of the compound, starting from N,N-dimethyl-N'-(5-bromo-2-pyridyl)ethylenediamine (2). In like manner, direct bromination of N,N-dimethyl-N'-(3-bromobenzyl)-N'-(2-pyridyl)ethylenediamine (V) gave a compound which is assigned the structure of N,N-dimethyl-N'-(3-bromobenzyl)-N'-(5-bromo-2-pyridyl)ethylenediamine (IX). The structure of N,N-dimethyl-N'-benzyl-N'-(5-chloro-2-pyridyl)ethylenediamine (VII) is based on its synthesis from 5-chloro-2-(N-benzyl)-aminopyridine and dimethylaminoethyl chloride. The intermediate 5-chloro-2-(N-benzyl)aminopyridine was prepared from 2-amino-5-chloropyridine and benzaldehyde in formic acid by the procedure of Tschitschibabin (5).

The antihistamine activities listed in Table I were obtained in guinea pigs by the histamine-aerosol technique (6), and are expressed as relative to Pyribenzamine, which has an assigned value of one. The highest activity is found in those derivatives halogenated in the 4-position of the benzyl group, and this

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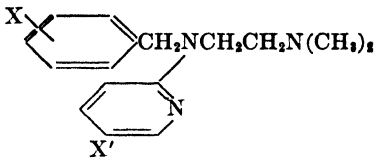
activity increases as the electronegativity of the substituent increases and its atomic weight decreases from iodo to fluoro. The 4-bromobenzyl derivative has approximately the same activity as Pyribenzamine but the 4-fluorobenzyl derivative is three to four times as active. Halogen substituents in the 2- or 3-position of the benzyl group or in the 5-position of the pyridyl group led to essentially inactive compounds. In the one example tested (compound IX), dihalogenation was also disadvantageous.

Four additional compounds structurally related to Pyribenzamine but not containing halogen were prepared and are reported here. Reaction of DPE with α-chloromethylnaphthalene and with n-hexyl bromide led, respectively, to the

TABLE I

HALOGENATED N,N-DIMETHYL-N'-BENZYL-N'-(2-PYRIDYL)ETHYLENEDIAMINES



COMPOUND	SUBSTITUENT		ACTIVITY (6)
	X	X'	
Pyribenzamine			1
I	4-F		3–4
II	4-Cl		2–3
III	2-Cl		<0.5
IV	4-Br		1
V	3-Br		<0.5
VI	4-I		0.3–0.5
VII		Cl	<0.5
VIII		Br	<0.5
IX	3-Br	Br	<0.5

formation of N,N-dimethyl-N'-(α-naphthylmethyl)-N'-(2-pyridyl)ethylenediamine (X) and N,N-dimethyl-N'-(n-hexyl)-N'-(2-pyridyl)ethylenediamine (XI). Reaction of 2-(N-benzyl)aminopyridine with chloroacetyl chloride followed by reaction with diethyl and with dimethylamine, respectively, led to the formation of N-benzyl-N-(2-pyridyl)-α-diethylaminoacetamide (XII) and N-benzyl-N-(2-pyridyl)-α-dimethylaminoacetamide (XIII) in low yield. The last two compounds are analogs of Pyribenzamine in which the dimethylaminoethyl group is replaced by a dialkylaminoacetyl group. Compounds X through XIII were inactive as histamine antagonists when tested on the isolated guinea pig ileum and, therefore, were not tested *in vivo*.

We are indebted to Dr. J. T. Litchfield, Jr., Mrs. Maxine Adams Peluso, and Miss Marion S. Jaeger of these Laboratories for the pharmacological data reported here.

EXPERIMENTAL[4]

4-Fluorobenzyl bromide. A solution of 110 g. (1.0 mole) of 4-fluorotoluene in 150 cc. of dry benzene was heated to reflux (90°) under an efficient condenser and irradiated with a 150-watt ultraviolet lamp. Liquid bromine (128 g.; 0.8 mole) was then added dropwise as rapidly as it was decolorized over a six-hour period. The reaction mixture was distilled at atmospheric pressure to yield 18.0 g. (80% recovery) of the excess 4-fluorotoluene used, b.p. 110–120°, n_D^{22} 1.4857, and 98.0 g. (65%) of 4-fluorobenzyl bromide, b.p. 195–202°, n_D^{22} 1.5480. The b.p. at 20 mm. was 93–95° which agrees with the literature value of 85° (15 mm.) (7). The product was stored over anhydrous potassium carbonate to remove traces of hydrogen bromide.

N,N-Dimethyl-N′-(4-fluorobenzyl)-N′-(2-pyridyl)ethylenediamine monohydrochloride. A suspension of 120 g. (5 moles) of sodium hydride in 2.5 liters of dry toluene was heated with stirring to 105° and maintained at this temperature while 830 g. (5 moles) of N,N-dimethyl-N′-(2-pyridyl)ethylenediamine (DPE) (4, 8) was added dropwise over a three-hour period. The reaction mixture was then heated at reflux for an additional three hours and cooled to 50°. At this temperature, 850 g. (4.5 moles) of 4-fluorobenzyl bromide was added dropwise at a rate sufficient to allow the resulting exothermic reaction to maintain the temperature of the mixture at 50–60°. The addition required three hours. The reaction mixture was stirred overnight at room temperature and then hydrolyzed cautiously with 750 cc. of water. The toluene layer was separated and concentrated. The residue was distilled *in vacuo* to yield 305 g. (excess used plus 27%) of DPE, b.p. 85–130° (0.15 mm.), n_D^{23} 1.5412, and 821 g. (67%) of N,N-dimethyl-N′-(4-fluorobenzyl)-N′-(2-pyridyl)ethylenediamine, b.p. 130–145° (0.25 mm.), n_D^{23} 1.5635. On standing for a short time at room temperature, the product crystallizes as long yellow needles. Recrystallization of these from hexane yielded colorless needles melting at 52–53°. The base was converted to its monohydrochloride in 86% yield by dissolving it in six parts by volume of toluene and adding 0.7 parts by volume of absolute ethanol containing one equivalent of hydrogen chloride. Recrystallization of the salt from toluene-alcohol (7:1) yielded colorless plates melting at 169.5–170.5°.

Anal. Calc'd for $C_{16}H_{20}FN_3 \cdot HCl$: C, 62.0; H, 6.8; N, 13.6; neutral equivalent, 310.
Found: C, 62.1; H, 6.8; N, 13.4; neutral equivalent, 305.

2-(4-Chlorobenzyl)aminopyridine. A solution of 30 g. (0.32 mole) of 2-aminopyridine and 46.8 g. (0.33 mole) of 4-chlorobenzaldehyde in 60 g. (1.3 moles) of 98–100% formic acid was heated at its reflux temperature for six hours. The reaction mixture was then worked up as described below for 5-chloro-2-benzylaminopyridine. The crude product weighed 73 g. (theory 70 g.) and melted at 93–95°. After recrystallization from dilute (1:1) aqueous alcohol the pure material melted at 100–102°.

Anal. Calc'd for $C_{12}H_{11}ClN_2$: C, 65.9; H, 5.1; N, 12.8; Cl, 16.2.
Found: C, 65.9; H, 5.2; N, 12.8; Cl, 16.4.

N,N-Dimethyl-N′-(4-chlorobenzyl)-N′-(2-pyridyl)ethylenediamine monohydrochloride. (a) In a single experiment in which the lithium derivative of 2-(4-chlorobenzyl)aminopyridine was treated with dimethylaminoethyl chloride (9), using the procedure described below for N,N-dimethyl-N′-benzyl-N′-(5-chloro-2-pyridyl)ethylenediamine, none of the desired compound was isolated.

(b) A solution of 40 g. (0.25 mole) of 2-bromopyridine and 100 g. (0.47 mole) of N,N-dimethyl-N′-(4-chlorobenzyl)ethylenediamine (10) in 106 g. of quinoline was heated at 140–145° for five hours. The reaction product was washed with 30% sodium hydroxide solution and distilled. That fraction, 9.5 g. (13%), which boiled at 145–170° (1.0 mm.), was separated and converted to the monohydrochloride by treating it with the theoretical quantity of alcoholic hydrogen chloride. After fractional crystallization from amyl alcohol (pentasol), the pure compound melted at 172–173.6°.

[4] All melting points are corrected. The microanalyses were carried out in these Laboratories under the direction of Dr. J. A. Kuck, to whom we are indebted for these data. The values reported represent the average of two values not differing by more than 0.3.

Anal. Calc'd for $C_{16}H_{20}ClN_3 \cdot HCl$: C, 58.9; H, 6.5; N, 12.9; Cl, 21.7.
Found: C, 58.5; H, 6.7; N, 12.7; Cl, 22.4.

(c) A mixture of 52.5 g. (0.317 mole) of N,N-dimethyl-N'-(2-pyridyl)ethylenediamine and 7.6 g. (0.33 mole) of lithium amide in 150 cc. of toluene was heated at reflux temperature with stirring for three hours. A solution of 48.3 g. (0.30 mole) of 4-chlorobenzyl chloride in 100 cc. of toluene was then added dropwise and heating continued for one hour. The reaction mixture was cooled, filtered, and distilled and that fraction which boiled at 178–185° (1.5 mm.) separated, 23.5 g. (27.1%). The light yellow oil was converted to the colorless monohydrochloride by the addition of one equivalent of alcoholic hydrogen chloride and recrystallization of the product from alcohol; 16.0 g., m.p. 172–173.6°.

Anal. Calc'd for $C_{16}H_{20}ClN_3 \cdot HCl$: Cl^-, 10.7. Found: Cl^-, 10.9.

N,N-Dimethyl-N'-(2-chlorobenzyl)-N'-(2-pyridyl)ethylenediamine monohydrochloride. To a solution of 0.055 mole of potassium amide in liquid ammonia was added 8.65 g. (0.053 mole) of DPE and then 50 cc. of toluene. The mixture was stirred and heated for ten minutes after all of the ammonia had been driven off. An 8.80-g. (0.053 mole) sample of 2-chlorobenzyl chloride was then added and the reaction mixture heated for an hour on a steam-bath. A second 50 cc. of toluene was then added and the reaction mixture was filtered. Distillation of the filtrate yielded 7.40 g. (49%) of N,N-dimethyl-N'-(2-chlorobenzyl)-N'-(2-pyridyl)ethylenediamine, b.p. 161–164° (1 mm.). This was converted to the monohydrochloride by dissolving it in ether and adding one equivalent of alcoholic hydrogen chloride. Two recrystallizations from isopropyl alcohol yielded colorless crystals, m.p. 203–204.5°, in 71% yield.

Anal. Calc'd for $C_{16}H_{20}ClN_3 \cdot HCl$: C, 58.9; H, 6.5; N, 12.9; N.E. 326.
Found: C, 58.5; H, 6.5; N, 12.7; N.E. 325.

N,N-Dimethyl-N'-(4-bromobenzyl)-N'-(2-pyridyl)ethylenediamine monohydrochloride. A suspension of the potassium salt of DPE in toluene was prepared by adding 0.78 g. (0.02 gram atom) of potassium to 100 cc. of liquid ammonia containing 80 mg. of black iron oxide, adding 3.3 g. (0.02 mole) of DPE when the potassium had all reacted, and removing the ammonia on the steam-bath after adding 75 cc. of dry toluene. To the cooled and stirred mixture was added 4.26 g. (0.021 mole) of 4-bromobenzyl chloride (11), and the reaction mixture was heated with stirring on the steam-bath for eleven hours. The mixture was filtered and concentrated to an oil. This concentrate was taken up in ether, and the etheral solution washed with water, dried over sodium sulfate, and concentrated. Distillation gave 2.96 g. (43%) of a yellow liquid boiling at 184–190° (1.0–0.5 mm.). Treatment of 2.42 g. of this distillate with an equivalent quantity of hydrogen chloride in absolute alcohol and precipitation with anhydrous ether gave 2 33 g. of the monohydrochloride which melted at 184–186° after crystallization from ethyl acetate.

Anal. Calc'd for $C_{16}H_{20}BrN_3 \cdot HCl$: C, 51.8; H, 5.7; N, 11.3.
Found: C, 51.7; H, 5.9; N, 11.3.

N,N-Dimethyl-N'-(3-bromobenzyl)-N'-(2-pyridyl)ethylenediamine monohydrochloride. A solution of 14.1 g. (0.086 mole) of DPE in 20 cc. of dry toluene was added to a solution of 0.086 mole of sodium amide in 50 cc. of liquid ammonia. The mixture was slowly heated to 100° to remove the ammonia. After cooling, 21.4 g. (0.086 mole) of 3-bromobenzyl bromide (12) in 50–60 cc. of toluene was added with stirring. After standing several hours at room temperature, the mixture was filtered and concentrated. Distillation of the residue yielded 3.5 g. (25% recovery) of DPE, b.p. 80–100° (1 mm.), and 16.3 g. (57%) of product, b.p. 176–178° (1 mm.). This was converted to the monohydrochloride in 80% yield by treatment with one equivalent of alcoholic hydrogen chloride. Addition of benzene to the alcohol solution and concentration gave the salt as a white solid. It melted at 169–170° after recrystallization from ethyl acetate containing a small amount of alcohol.

Anal. Calc'd for $C_{16}H_{20}BrN_3 \cdot HCl$: N, 11.3; N.E. 371.
Found: N, 11.3; N.E. 376.

N,N-Dimethyl-N'-(4-iodobenzyl)-N'-(2-pyridyl)ethylenediamine monohydrochloride. The preparation of 4-iodobenzyl bromide by the bromination of 4-iodotoluene in the absence of

solvent has been reported (13). It was found more convenient to carry out the reaction in refluxing carbon tetrachloride under irradiation with ultraviolet light. A stirred mixture of 2.29 g. (0.095 mole) of sodium hydride and 16.5 g. (0.1 mole) of DPE in 300 cc. of dry toluene was heated slowly to reflux for twenty to thirty minutes until reaction was complete. After the mixture had been cooled, 28.3 g. (0.095 mole) of 4-iodobenzyl bromide was added, and the resulting mixture was heated with stirring on the steam-bath for two hours. The cooled and filtered solution was washed three times with water and concentrated under reduced pressure. Distillation gave 23.61 g. (65%) of a viscous, yellow fraction boiling at 194–207° (1 mm.), n_D^{25} 1.6144. Treatment of 20.2 g. of this liquid with one equivalent of hydrogen chloride in alcohol and precipitation by the addition of ether gave 20.96 g. of the monohydrochloride melting at 191–195°. Crystallization from methyl ethyl ketone or from ethyl acetate and absolute alcohol gave fine white needles, m.p 200–202°.

Anal. Calc'd for $C_{16}H_{20}IN_3 \cdot HCl$: N, 10.1; Cl, 8.5.

Found: N, 9.9; Cl, 8.4.

5-Chloro-2-benzylaminopyridine. To 40 g. (0.31 mole) of 2-amino-5-chloropyridine (14) was added 60 g. (1.3 moles) of anhydrous formic acid and 34 g. (0.32 mole) of redistilled benzaldehyde. The reaction mixture was heated at reflux temperature for sixteen hours, cooled, and poured into 100 g. of 50% sodium hydroxide and 200 g. of ice. The solid product was filtered and dried in the air; yield, 60.6 g. (89%). After treatment with Darco and recrystallization from a commercial naphtha, a colorless product was obtained which softened at 94° and melted at 114–115.2°.

Anal. Calc'd for $C_{12}H_{11}ClN_2$. C, 65.9; H, 5.1; N, 12.8.

Found: C, 65.7; H, 4.8; N, 12.5.

N,N-Dimethyl-N'-benzyl-N'-(5-chloro-2-pyridyl)ethylenediamine monohydrochloride. To 21.8 g. (0.1 mole) of 5-chloro-2-benzylaminopyridine in 100 cc. of boiling toluene was added 2.5 g. (0.11 mole) of lithium amide, and the reaction mixture was heated at reflux with stirring for two hours. A solution of 11.8 g. (0.11 mole) of dimethylaminoethyl chloride in 50 cc. of toluene was then added dropwise over fifteen minutes and the stirred suspension heated at reflux for an additional two hours. After cooling, the mixture was filtered and concentrated by distillation. The residue was then distilled and that fraction boiling between 163° (20 microns) and 185° (50 microns) collected. After standing overnight the oil was filtered to remove some solid impurity; yield, 19.8 g. (68%). Treatment of this material with one equivalent of alcoholic hydrogen chloride gave 21 2 g. of the monohydrochloride which melted at 179–180° after recrystallization from acetone.

Anal. Calc'd for $C_{16}H_{20}ClN_3 \cdot HCl$: C, 58.9; H, 6.5; N, 12.9; Cl (total), 21.7; Cl (ion), 10.9.

Found: C, 58.9; H, 6.4; N, 12.8; Cl (total), 21.6; Cl (ion), 10.9.

N,N-Dimethyl-N'-benzyl-N'-(5-bromo-2-pyridyl)ethylenediamine monohydrochloride. To a solution of 10.8 g. (0.037 mole) of N,N-dimethyl-N'-benzyl-N'-2-pyridylethylenediamine hydrochloride (4) and 3.1 cc. (0.037 mole) of hydrochloric acid (*d.* 1 19) in 50 cc. of water was added, all at once, 5.9 g. (0.037 mole) of bromine. A reaction occurred, resulting in the formation of an orange gum. After brief heating on the steam-bath and vigorous shaking the gum dissolved and a clear solution resulted. The solution was made alkaline with solid sodium hydroxide and the resulting base extracted with 200 cc. of benzene in three portions. The extracts were concentrated and the residue (12.4 g.) treated with one equivalent of alcoholic hydrogen chloride. The resulting solution was diluted with 150 cc. of benzene and concentrated until crystallization occurred; yield, 8.4 g. (61%), m.p. 180–182°.

Anal. Calc'd for $C_{16}H_{20}BrN_3 \cdot HCl$: N, 11.3. Found: N, 11.6.

The product prepared from benzyl chloride and N,N-dimethyl-N'-(5-bromo-2-pyridyl)-ethylenediamine (2) in low yield was identical by mixed melting point with that prepared above.

N,N-Dimethyl-N'-(3-bromobenzyl)-N'-(5-bromopyridyl)ethylenediamine monohydrochloride. An 8.14-g. (0.022 mole) sample of N,N-dimethyl-N'-(3-bromobenzyl)-N'-(2-pyridyl)-ethylenediamine was dissolved in 30 cc. of 0.75 *N* hydrochloric acid (0.022 mole) and treated with 3.5 g. (0.022 mole) of bromine as in the preparation of N,N-dimethyl-N'-benzyl-N'-

(5-bromo-2-pyridyl)ethylenediamine above. The product (7.8 g.; 86%) was isolated as in the previous example and converted to its monohydrochloride. After recrystallization from ethyl acetate and methyl ethyl ketone the pure salt melted at 146.5–147.5°.

Anal. Calc'd for $C_{16}H_{19}Br_2N_3 \cdot HCl$: N, 9.3; Cl, 7.9.

Found: N, 9.6; Cl, 8.0.

N,N-Dimethyl-N'-(α-naphthylmethyl)-N'-(2-pyridyl)ethylenediamine monohydrochloride. A solution of 10.0 g. (0.06 mole) of DPE in 50 cc. of toluene was added to a solution of 0.09 mole of sodium amide in liquid ammonia. The excess ammonia was then removed by heating and a solution of 11.0 g. of α-chloromethylnaphthalene (15) in 100 cc. of toluene was added. The reaction mixture was heated with stirring on the steam-bath for four hours, cooled, hydrolyzed with water, and the toluene layer separated. This was concentrated and distilled through a wide-bore head to give 2.0 g. (20%) of recovered DPE and 4.95 g. (27%) of the product, b.p. 200° (1 mm.). The material solidified on standing and after crystallization from ether-petroleum ether melted at 95°. Treatment with one equivalent of alcoholic hydrogen chloride and precipitation of the salt with ether gave a monohydrochloride which melted at 224–226° after four crystallizations from isopropanol.

Anal. Calc'd for $C_{20}H_{23}N_3 \cdot HCl$: C, 70 3; H, 6.8; N, 12.1; N.E., 342.

Found· C, 69.7; H, 7 3; N, 11.7; N.E., 342.

N,N-Dimethyl-N'-(n-hexyl)-N'-(2-pyridyl)ethylenediamine monohydrochloride. A stirred mixture of 6.0 g. (0 25 mole) of sodium hydride and 41.0 g. (0.25 mole) of DPE in 250 cc. of dry toluene was heated at 95° for forty minutes, then cooled to 57° and 33 g. (0.20 mole) of *n*-hexyl bromide added. The reaction mixture was further heated at 95° for eighteen to twenty hours, cooled, and hydrolyzed with 100 cc of water. The organic layer was separated, concentrated, and distilled to give 34 g. (68%) of crude product boiling at 110–150° (2 mm.). This was refractionated to yield 18 9 g (38%) of product boiling at 136–146° (1 mm.), $n_D^{31.5}$ 1 5090. This was converted to the monohydrochloride by treatment with one equivalent of alcoholic hydrogen chloride and evaporation of the solution to dryness. After two crystallizations from benzene, the colorless salt melted at 104–105°. A satisfactory analysis for carbon was not obtained for this compound.

Anal. Calc'd for $C_{15}H_{27}N_3 \cdot HCl$: C, 63.0; H, 9.9; N, 14.7; N.E., 286.

Found· C, 61.8; H, 9 6, N, 14.5; N.E., 288.

N-Benzyl-N-(2-pyridyl)-α-diethylaminoacetamide hydrochloride (16). A mixture of 24.6 g. (0.133 mole) of 2-benzylaminopyridine (5) and 13.2 g. (0.133 mole) of triethylamine in 250 cc. of anhydrous ether was stirred and chilled in an ice-bath while a solution of 14.9 g. (0.133 mole) of chloroacetyl chloride in 250 cc of ether was added dropwise in about ninety minutes. After stirring one hour longer, the mixture was filtered and 177 cc (1.7 mole) of diethylamine added to the filtrate with stirring under anhydrous conditions The solution darkened and diethylamine hydrochloride slowly precipitated. This was removed after forty-eight hours and the filtrate evaporated in a water-bath at aspirator pressure. The residue was redissolved in 100 cc. of absolute alcohol and treated with a solution of 29 g. of 90% picric acid in 500 cc. of absolute alcohol to precipitate slowly unreacted 2-benzylaminopyridine as a crystalline monopicrate. After standing six days at room temperature, the solution was decanted and the 2-(N-benzyl)aminopyridine picrate recrystallized from methanol, m.p. 115–116°.

Anal. Calc'd for $C_{18}H_{23}N_3O \cdot C_6H_3N_3O_7$· picric acid, 43 5. Found: picric acid, 43.4.

On addition of more picric acid to the decantate and scratching, the picrate of the desired product precipitated slowly. This was separated after several hours, suspended in a mixture of water and chloroform and treated with an excess of sodium hydroxide. The chloroform layer was concentrated, and the residue was converted to a hydrochloride salt by solution in ether and treatment with one equivalent of dry hydrogen chloride in ether. The salt was purified by digestion with ether, concentration of a methanol-benzene solution, and crystallization from acetone; yield, 4.1 g. (10%), m.p. 147–148.5°.

Anal. Calc'd for $C_{18}H_{23}N_3O \cdot HCl$: C, 64 7; H, 7.2; N, 12.6.

Found: C, 64.9; H, 7.4; N, 12 8.

N-Benzyl-N-(2-pyridyl)-α-dimethylaminoacetamide hydrochloride. This compound was

prepared as described for the diethyl derivative on a 0.133-mole scale using a solution of 154 g. (3.4 moles) of dimethylamine in 500 cc. of dry ether. The picrate prepared from the reaction product was an uncrystallizable oil. Conversion to the free base and subsequently to a monohydrochloride salt gave a solid which was purified by thorough drying and repeated crystallization from acetone; yield, 4.0 g. (10%), m.p. 181–184°.

Anal. Calc'd for $C_{16}H_{19}N_3O \cdot HCl$: C, 62.8; H, 6.6; N, 13.7.

Found: C, 62.6; H, 6.8; N, 13.4.

SUMMARY

The preparation of one dihalogenated and eight monohalogenated derivatives of N,N-dimethyl-N′-benzyl-N′-(2-pyridyl)ethylenediamine (Pyribenzamine) and four other compounds structurally related to it are reported.

The physiological activities as histamine antagonists of all compounds are given.

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[Contribution from the Chemotherapy Division of the Stamford Research Laboratories, American Cyanamid Company]

ANTIHISTAMINE AGENTS. V. 2-SUBSTITUTED ETHYLAMINES

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At the time these compounds were prepared, the most active known antihistamine agents were 2-dimethylaminoethyl benzohydryl ether (Benadryl) (1), and N,N-dimethyl-N′-benzyl-N′-2-pyridylethylenediamine (Pyribenzamine) (2). Consequently, the structures of these compounds bear varying degrees of resemblance to those established agents. Each of the eleven compounds prepared has the general formula R-CH_2-CH_2-NR_1R_2 in which R_1 and R_2 may be methyl, benzyl, or hydrogen. The R group includes 2-pyrazylamino-, 2-pyrazyloxy-, 2-amino-4-pyrimidyloxy-, 5-chloro-2-pyrimidyloxy-, 5-chloro-2-pyrimidylmercapto-, 2-pyridyloxy-, *o*-nitranilino-, 2-benzothiazolyloxy-, N-benzyl-2-pyridylamino-, and benzohydryloxy-.

Most of the compounds were prepared using the Williamson ether synthesis. Each of the dimethylaminoethoxy compounds was made by dissolving sodium metal in an excess of commercial dimethylaminoethanol and treating the resulting solution with the appropriate aromatic halide. In those cases where the reagent alcohol was less readily obtained, it was dissolved in toluene, where it was converted to the sodium salt and thence etherified. A modification of this for the preparation of substituted amines involves the use of a substituted sodamide, sodio-2-benzylaminopyridine, after the method used by Whitmore (3). In two cases 2,5-dichloropyrimidine was used as the halide. The product is designated as 5-chloro-2-pyrimidyl because English (4) prepared 5-chloro-2-methylaminopyrimidine in 87% yield by a similar reaction. English's compound was identified by an independent synthesis. Two secondary amines were prepared in good yields by the direct action of amines on halogen compounds, and one was prepared by treatment of a primary amine with benzaldehyde and subsequent hydrogenation of the Schiff's base formed.

None of the compounds was more active than Benadryl when tested *in vitro* against histamine spasm of guinea pig gut.

EXPERIMENTAL

All melting points are corrected. All analyses except the neutral equivalents are the average of two or more determinations. Combustion analyses were carried out under the direction of Dr. J. A. Kuck; the pharmacology was studied under the supervision of Dr. J. T. Litchfield, Jr.

2-(2-Dimethylaminoethyl)aminopyrazine. When 3.5 g. of chloropyrazine and 5.3 g. of 2-dimethylaminoethylamine were heated for three hours in a bath at 130–140° and then treated with 40% sodium hydroxide, an oil formed. When this was removed by washing with ether, it gave an oil, 2.6 g. of which distilled 120–124° at 4 mm., a 51% yield. The picrate from this, after repeated crystallization from ethanol, melted 157–159°.

Anal. Calc'd for $C_{14}H_{17}N_7O_7$: C, 42.53; H, 4.33; N, 24.80.
Found: C, 43.12; H, 4.77; N, 24.54.

2-(2-Dimethylaminoethoxy)pyrazine. A solution of 4 g. of sodium in 125 cc. of 2-dimethylaminoethanol was treated with 20 g. of chloropyrazine and stirred on the steam-bath for ninety minutes. The cooled liquid was filtered and vacuum distilled. A 21.7-g. cut boiling 80–89° at 5 mm. was collected (74%). The picrate melted at 136–138°.

Anal. Calc'd for $C_{14}H_{16}N_6O_8$: N, 21.21. Found: N, 21.54.

4-(2-Dimethylaminoethoxy)-2-aminopyrimidine. A solution of 4.6 g. of sodium in 200 cc. of 2-dimethylaminoethanol was treated with 25.9 g. of 2-amino-4-chloropyrimidine and then stirred on a steam-bath for an hour. The cooled, filtered, vacuum-concentrated product was continuously extracted with ethyl acetate. Three crystallizations from ethyl acetate gave 14.5 g. (40%) of tan crystals melting at 110–111°.

Anal. Calc'd for $C_8H_{14}N_4O$: N, 30.75. Found: N, 30.51.

2-(2-Dimethylaminoethylmercapto)-5-chloropyrimidine. Using essentially the method of Suter (5), 2-dimethylaminoethylmercaptan was made in 38% yield. The product distilled at 40–50° at 10–20 mm. pressure, and it gave a monohydrochloride which melted at 159–161° after recrystallization from isopropanol.

A mixture of 0.43 g. of sodium and 2 g. of 2-dimethylaminoethylmercaptan was stirred for seventeen hours at room temperature in toluene. The white suspension was then treated with 2.8 g. of 2,5-dichloropyrimidine and heated two hours on the steam-bath. Cooling, filtration, and vacuum distillation produced 2.22 g. (50%) of a light yellow oil boiling at 110–120° at 2 mm. The hydrochloride of this, recrystallized from isopropanol, melted at 188–190°. The picrate melted at 177–179°.

Anal. Calc'd for $C_8H_{13}Cl_2N_3S$: C, 37.80; H, 5.15; N, 16.53.
Found: C, 37.83; H, 6.03; N, 15.29.

2-(2-Dimethylaminoethoxy)-5-chloropyrimidine. A solution of 1.23 g. of sodium in 50 cc. of 2-dimethylaminoethanol was treated with 8 g. of 2,5-dichloropyrimidine and heated on a steam-bath for an hour. The product was chilled, filtered and concentrated by evaporation *in vacuo.* The hydrochloride was formed by passing dry hydrochloric acid into an alcoholic solution of the crude product followed by precipitation by dilution with ether. Recrystallization from isopropanol gave 8 g. (62%) of shiny white crystals melting 180–182°. The picrate melts 160–161°.

Anal. Calc'd for $C_8H_{13}Cl_2N_3O$: C, 40.35; H, 5.50; N, 17.65.
Found: C, 41.39; H, 6.18; N, 17.32.

2-(2-Benzylaminoethoxy)pyridine. A solution of 15.1 g. of 2-benzylaminoethanol and 15.8 g. of 2-bromopyridine in 50 cc. of toluene was added dropwise to a suspension of 5.5 g. of potassamide in toluene. The reaction was run hot, and ammonia evolved rapidly. After twenty hours at reflux temperature the mixture was cooled, filtered, and extracted with 5% hydrochloric acid. When this was made alkaline again and extracted and distilled, two separate products were obtained. One was 2 8 g. of oil boiling 115–120° at 0.5 mm. which is probably N-benzyl-N-(2-pyridyl)aminoethanol. It did not form a hydrochloride with pentachloroethane but did react with sodium. A second cut was 8.2 g. (35%) boiling 135–137° at 0.5 mm. This was heated with 40 cc. of pentachloroethane for thirty minutes on the steam-bath to produce 6.0 g. of white crystals. These were recrystallized four times from ethyl acetate to produce colorless plates melting at 174–175°.

Anal. Calc'd for $C_{14}H_{17}ClN_2O$: C, 63.51; H, 6.47; N, 10.58.
Found: C, 63 63; H, 6.73; N, 10.26.

2-(2-Dimethylaminoethoxy)pyridine. This product was prepared in 40% yield by the action of 5 g. of 2-bromopyridine on a solution of 0.73 g. of sodium in 30 cc. of 2-dimethylaminoethanol. The product was 2 g. of oil boiling 80–90° at 0.3 mm. This was made into the dipicrate which melted at 155°.

Anal. Calc'd for $C_{21}H_{20}N_8O_{15}$: C, 40.32; H, 3.22; N, 17.92.
Found: C, 40.38; H, 3.54; N, 17.81.

Bis-(2-N-benzyl-N-2-pyridylaminoethyl) ether. Sodamide, prepared from 1.3 g. of sodium in liquid ammonia containing a trace of ferric nitrate, was treated with 10.4 g. of ben-

zyl-2-pyridylamine. The liquid ammonia was replaced with dry toluene and 4.0 g. of bis-(2-chloroethyl) ether was added at room temperature. This was heated for four hours on the steam-bath before hydrolysis. Many unsatisfactory ways of purifying the product were tried before it was found that the difficult impurities were removed by prolonged steam distillation. The oil remaining behind was recrystallized from ethanol and a little Darco to give 0.61 g. of white crystals melting at 99–100° (5.5%).

Anal. Calc'd for $C_{28}H_{30}N_4O$: C, 76.68; H, 6.90; N, 12.78.

Found: C, 76.29; H, 7.03; N, 12.97.

2-Dimethylaminoethyl-o-nitraniline. When 52.5 g. of *o*-chloronitrobenzene, 29.3 g. of 2-dimethylaminoethylamine, and 70 g. of sodium carbonate were refluxed together for four hours, an orange mixture, largely solid, resulted. The product was steam distilled, and the red oil so obtained was vacuum distilled; 57 g. (83%) was collected, boiling 129–135° at 2 mm. A hydrochloride was prepared from this and recrystallized from ethyl acetate. After sublimation at 1 mm. pressure the salt melted at 186–188°.

Anal. Calc'd for $C_{10}H_{16}ClN_3O_2$: C, 48.88; H, 6.51; N, 17.10; N.E. 246.

Found: C, 48.77; H, 6.87; N, 16.71; N.E., 239.

2-(2-Dimethylaminoethoxy)benzothiazole. A solution of 0.68 g. of sodium in 30 cc. of 2-dimethylaminoethanol was treated with 5 g. of 2-chlorobenzothiazole during ten minutes. The mixture was heated for an hour on a steam-bath, then chilled and filtered. The excess solvent was evaporated *in vacuo*, and the light yellow, oily residue was separated from an insoluble gum by extraction with ether. Concentration of the ether solution and distillation yielded 4.05 g. (62%) boiling from 147–155° at 4 mm. A solution of 3.39 g. of this liquid in alcohol was treated with dry hydrogen chloride, and the hydrochloride was precipitated by the addition of ether. Crystallization of the precipitate from alcohol gave 1.54 g. of glistening plates, m.p. 189–191°.

Anal. Calc'd for $C_{11}H_{15}ClN_2OS$: C, 51.05; H, 5.84; N, 10.83.

Found: C, 51.20; H, 6.09; N, 10.76.

2-Aminoethyl benzohydryl ether. A hot solution of 1.6 g. of sodium in 50 cc. of ethanolamine was treated with 17.0 g. of bromodiphenylmethane. The resulting solution was kept hot for an hour and then concentrated *in vacuo* to 38 cc. volume. This was drowned in 200 cc. of water and extracted with ether. The ether extract was vacuum distilled to yield 11.3 g. (72%) of a yellow oil boiling at 150–153° at 0.3 mm. This oil crystallized in ether and was recrystallized from ether-ligroin mixtures, m.p. 73–74°. Pharmacology, but no chemistry of this compound has been reported (6).

Anal. Calc'd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16; N.E., 227.

Found: C, 79.26; H, 7.66; N, 5.89; N E., 232.

2-Benzylaminoethyl benzohydryl ether. When 23 g. of 2-aminoethyl benzohydryl ether and 10 6 g. of benzaldehyde were heated overnight in 100 cc. of boiling toluene, 1.8 cc. of water was produced and collected in a Dean trap. Attempts to reduce the product at 3 atm. hydrogen pressure failed over platinum oxide and over palladium on charcoal. When the mixture was heated to 115° and shaken over two teaspoonsful of Raney nickel with high pressure hydrogen it absorbed 70% of the theoretical hydrogen. The product was filtered and distilled to give two cuts. The first was 12.1 g boiling 62–147° at 0.1 mm., and it is unidentified. The second was 10.1 g. (25%) of yellow oil boiling 182–204° at 0.4–0.6 mm.; n_D^{30} 1.5912. This was converted to the hydrobromide by treatment with alcoholic hydrobromic acid. It was recrystallized from absolute alcohol, m.p. 181–182°.

Anal. Calc'd for $C_{22}H_{24}BrNO$: C, 66.33; H, 6.07; N, 3.52; N.E., 398.

Found: C, 66.29; H, 6.26; N, 3 59; N.E., 406.

SUMMARY

The preparation and some properties of eleven new 2-substituted ethylamines are recorded.

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[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

REACTIONS OF ATOMS AND FREE RADICALS IN SOLUTION. XIX. THE COMPARATIVE REACTIVITIES OF DOUBLE BONDS IN CYCLIC OLEFINS TOWARD FREE RADICALS

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The photochemical free-radical chain addition of a polyhalomethane (*e.g.*, bromotrichloromethane) to olefins may be represented as follows (1):

$$BrCCl_3 + h\nu \rightarrow Br\cdot + Cl_3C\cdot$$

1. $RCH{=}CH_2 + Cl_3C\cdot \rightarrow \cdot CHRCH_2CCl_3$
2. $\cdot CHRCH_2CCl_3 + BrCCl_3 \rightarrow RCHBrCH_2CCl_3 + Cl_3C\cdot$

Steps 1 and 2 constitute the cycle, and are both critical for chain continuation. Thus, if the rate of addition of the free trichloromethyl radicals (step 1) is slow, these radicals accumulate until their concentration becomes so high that the chain is terminated by free-radical dimerization and the formation of hexachloroethane. On the other hand, if step 2 is slow, the secondary free radicals formed in step 1 may "dimerize" or add to other molecules of the olefin to yield "polymers" containing two or more molecules of olefin per molecule of bromotrichloromethane.

The relative reactivities of cyclic olefins with respect to free-radical addition. In order to compare the reactivities of olefins with respect to free-radical addition in step 1, reagents which assure the success of step 2 must be selected. It has been demonstrated[1] that bromotrichloromethane is such a reagent, for the bromine atom is easily extracted from the molecule by the secondary free radical; the product thus formed is the one-to-one adduct of the olefin and bromotrichloromethane.

The relative reactivities of two olefins in step 1 may be ascertained by allowing a one-to-one mixture of the olefins to react with a large excess of bromotrichloromethane. The reaction is allowed to proceed until about 25–50% of the olefin present has reacted, and the amount of each of the two adducts is then determined. The relative reactivities of several cyclic olefins with respect to addition of a free trichloromethyl radical (step 1) are given in Table I. The reactivity of 1-octene is taken as unity.

In all instances, the compound containing a five-membered unsaturated ring proved to be more reactive than the corresponding six-membered ring compound. Thus, cyclopentadiene is more reactive than cyclohexadiene; cyclopentene is more reactive than cyclohexene; and bicycloheptene is more reactive than bicyclooctene. The relative reactivities are thus correlated with the relative differences

[1] Kharasch, Sage, and Urry (unpublished work), have measured the relative reactivities of a series of acyclic olefins. Kharasch, Jerome, and Benca (unpublished work), have measured the relative reactivities of a series of acetylenes.

in strain between the unsaturated and the corresponding saturated ring compound. The conjugated olefins cyclopentadiene, cyclohexadiene, and indene (where the ring strain is the greatest) are more reactive than the nonconjugated olefins.

The relative reactivities of the free radicals formed in step 1 with bromotrichloromethane. In order to measure the relative reactivities of the secondary free radicals with respect to bromotrichloromethane (step 2) the reaction kinetics and the energy of activation required for this step were studied. It was observed that styrene, which adds bromotrichloromethane well at 60°, and which, at that temperature, is at least one hundred times as reactive as octene, hardly reacts at 20°. On the other hand, allyl chloride and cyclohexene give good yields of addition product even at 10°. Furthermore, styrene (which does not react with bromotrichloromethane at 20°) inhibits the reaction of allyl chloride or bicycloheptene

TABLE I

THE RELATIVE REACTIVITIES OF SOME CYCLOALKENES WITH RESPECT TO THE ADDITION OF A FREE TRICHLOROMETHYL RADICAL

4.5	Cyclopentadiene
4.0	1,3-Cyclohexadiene
3.0	Indene
1.2	Bicyclo[2.2.1]heptene-2
1.05	Dicyclopentadiene
1.0	1-Octene
0.80	Cyclopentene
0.24	Cyclohexene
0.11	Bicyclo[2.2.2]octene-2
0.06	Butadiene sulfone

at 20°, although either one of these compounds alone reacts quite well with bromotrichloromethane at that temperature. Thus, there is a peculiar inhibition of free-radical addition by a substance which itself adds well at higher temperatures. These phenomena may be explained as follows. Styrene adds free radicals rapidly in step 1, outrunning all other competing olefins; it thereby uses up the free radicals and prevents the other olefins from capturing them. However, at low temperatures styrene does not continue the chain (step 2) at an appreciable rate. It thus effectively prevents the addition of other olefins which by themselves could readily undergo step 2. These qualitative observations indicate that there is a close connection between reaction rate and chain propagation.

The rates of the over-all reaction for several olefins at various temperatures were measured. The rate curves fit those to be expected for zero-order reactions; that is, the change in olefin concentration with time is constant. The rates are determined for the first half of the reaction period, because in the latter half there is a slight decrease in rate due to the high concentrations of the solutions used. Table II lists the rates obtained in the various over-all reactions. However, when the logarithms of the rates are plotted against the reciprocals of the absolute

temperatures in order to determine the energy of activation the curves obtained are not straight lines. Table III lists the values of the pseudo energies of activation as calculated from the rates measured in the indicated temperature intervals. Thus quantitative data concerning step 2 cannot be obtained by the method indicated.

The large variation in apparent, or pseudo activation energy (Table III) is worthy of special comment. Several alternative kinetic equations have been derived for the addition of bromotrichloromethane to olefins. The details of the kinetics so derived depend on the reactions (or reaction) chosen as the chain terminating steps. It is easily possible to obtain a kinetic equation which will agree with the experimental observation that the rate of addition of bromotrichloromethane to the olefin is independent of olefin concentration. But, the activation energy associated with such a mechanism is a linear function of the activation energies of some of the individual reactions steps (equations 1 and 2, and chain terminating steps). The calculated activation energy is thus essentially temperature independent. Since the so called "pseudo activation energy" for the addition of bromotrichloromethane to styrene decreases, over a temperature interval of thirty degrees, from 23 Kcal/mole to almost zero, any simple kinetic expression fails to account for one of the most significant features of the reaction. Perhaps, the chain terminating step for the reaction changes over the temperature interval investigated, or traces of impurities have a greater effect at some temperatures and not at others, or, perhaps, some new principle is here involved. In any event, it is clear that the apparent activation energy cannot at

TABLE II

RATE OF REACTION[a] OF OLEFINS WITH BROMOTRICHLOROMETHANE

	10°	20°	30°	40°	50°
Styrene		0.004	0.09	0.16	0.17
Octene		0.07	0.59	0.70	1.11
Cyclohexene		0.07	0.11	0.14	0.19
Allyl chloride	0.03	0.08	0.14		
Bicycloheptene	0.14	0.26	0.27		

[a] Units of rate are moles/hour.

TABLE III

EXPERIMENTAL PSEUDO ACTIVATION ENERGIES IN KG. CAL. PER MOLE

	10-20°	20-30°	30-40°	40-50°
Styrene		23	4.8	0.5
Octene		16	1.4	3.4
Cyclohexene		3.5	2.2	2.7
Allyl chloride	7.2	4.2		
Bicycloheptene	4.4	0.5		

present be associated with any single step or any known combination of steps in the reaction. Further, the work presented here suggests that the activation energies for all chain reactions must be carefully inspected in each individual case to determine whether or not they are strongly temperature dependent; if they are, their interpretation is questionable. In the present instance, a complete understanding of the temperature dependence of the activation energy must await further intensive investigation.

Properties of adducts of bromotrichloromethane and cyclic olefins. The one-to-one adducts of bromotrichloromethane and the cyclic olefins have properties similar to those of the corresponding adducts of the simple aliphatic olefins. All except those obtained from bicycloheptene, bicyclooctene, or dicyclopentadiene, when treated with bases lose hydrogen halide with relative ease. Thus, the addition compound (I) formed from butadiene sulfone can be titrated with cold alcoholic potassium hydroxide. By this treatment one molecule of hydrogen chloride and one molecule of hydrogen bromide are removed. The product is a conjugated diene (II) showing a narrow absorption peak at 2610 Å with a molecular absorption coefficient of 19,000 (2). The adduct of bromotrichloromethane and cyclohexene, 1-trichloromethyl-2-bromocyclohexane (III) when treated with cold sodium ethoxide in absolute ethyl alcohol yields a conjugated diene (IV) showing a broad absorption peak at 2500 Å with a molecular absorption coefficient of 12,000 (Figure 1). Two compounds (a solid, 32% yield, and an oil, 68% yield) were isolated from the product formed by the addition of bromotrichloromethane to 1,3-cyclohexadiene. Compounds V and VI are respectively the 1,2 and 1,4 adducts anticipated. When either the oil or the solid is titrated at 50° with alcoholic potassium hydroxide the same product, 3-dichloromethylene-6-hydroxy-cyclohexene (VIIa), is obtained. This compound has a narrow absorption peak at 2530 Å with a molecular absorption coefficient of 13,000 (Figure 1). When either the solid or the oil is titrated with cold sodium ethoxide in absolute ethyl alcohol the same alkoxy product is obtained. It is 3-dichloromethylene-6-ethoxy cyclohexene (VIIb), and is contaminated with some of the corresponding hydroxy compound (VIIa). The absorption curve of (VIIb) is practically identical with that of (VIIa); it shows a narrow peak at 2530 Å with a molecular absorption coefficient of 13,000.

Thus, the saturated cyclic adducts (I) and (III) readily lose one molecule of hydrogen bromide and one molecule of hydrogen chloride, to yield dienes. The hydrogen bromide lost contains the available hydrogen atom farthest from the trichloromethyl group. The saturated non-cyclic adducts lose only one molecule of hydrogen bromide containing the hydrogen atom nearest to the trichloromethyl group. (For example the adduct of bromotrichloromethane and 1-octene, 1,1,1-trichloro-3-bromononane, yields 1,1,1-trichlorononene-2[2] when treated with either cold sodium ethoxide or alcoholic potassium hydroxide at 50°.)

In the unsaturated cyclic adducts like V or VI where an allylic bromine is

[2] The position of the double bond was determined by ozonization, the products being heptaldehyde and chloral.

present, the bromine atom is first replaced by the base (hydroxide or ethoxide ion) and subsequently one molecule of hydrogen chloride is removed; a hydroxy diene or ethoxy diene is thus formed.

The addition compounds of bromotrichloromethane with bicycloheptene (VIII) or bicyclooctene (IX) do not react with alcoholic potassium hydroxide at the

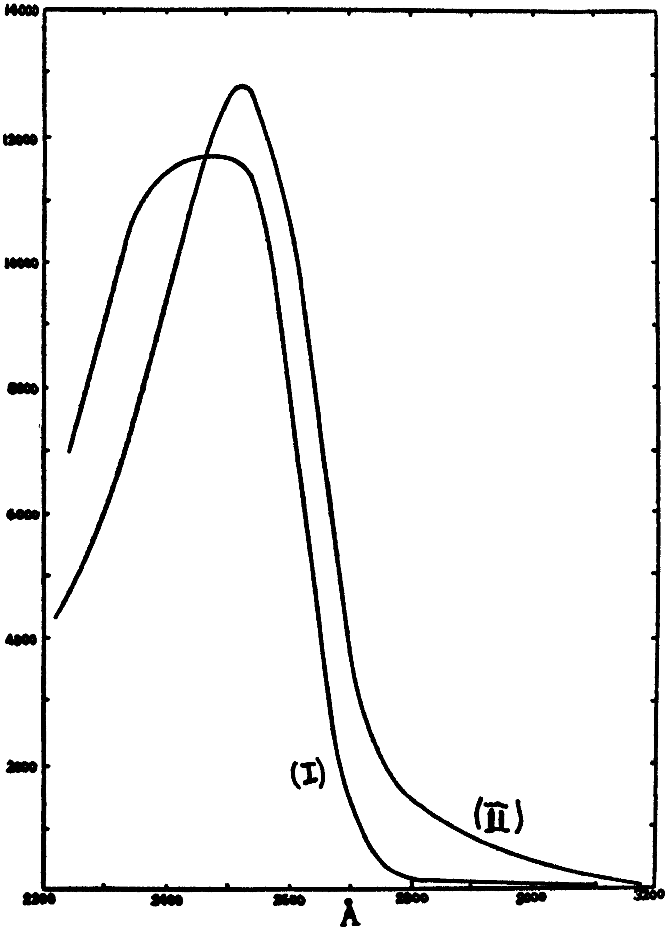
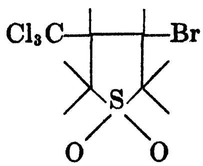
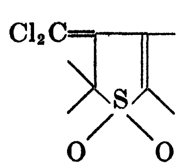


FIGURE 1. (I) 3-Dichloromethylenecyclohexene (Compound IV); (II) 6-Hydroxy-3-dichloromethylenecyclohexene (Compound VIIa).

boiling point of ethyl alcohol and are in general quite stable with respect to loss of hydrogen halide. These results are consistent with Bredt's hypothesis that a double bond at a bridge head [such as would be required by loss of hydrogen bromide from the 2 and 3 positions (IX)] is not readily formed. Loss of hydrogen bromide from the 1 and 2 positions (IX) should not readily occur in view of the behavior of the saturated cyclic adducts described above.



(I)



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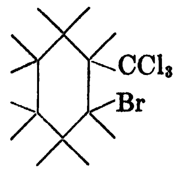
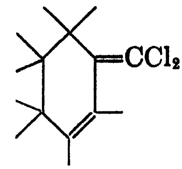
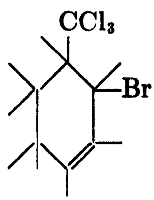


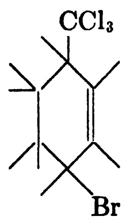
(III)



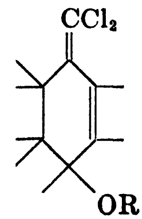
(IV)



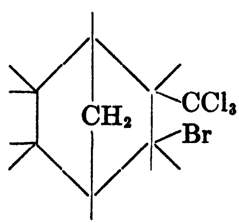
(V)



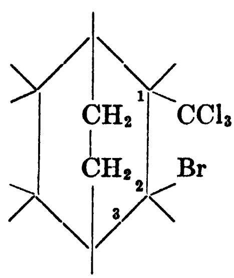
(VI)



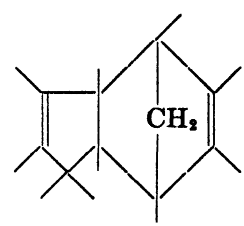
(VIIa) R = H
(VIIb) R = C_2H_5



(VIII)



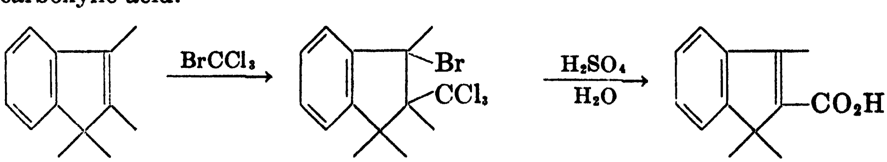
(IX)



(X)

Dicyclopentadiene (X) has two double bonds; only one of them, however, adds bromotrichloromethane. The reactive one is probably the bicycloheptene double bond, for the addition compound does not react with alcoholic potassium hydroxide, and the reactivity of the olefin is closer to that of bicycloheptene than to that of cyclopentene (see Table I).

The addition compound of bromotrichloromethane and indene is 2-trichloromethyl-3-bromoindane (XI), for it is hydrolyzed by 70% sulfuric acid to indene-2-carboxylic acid.



(XI)

EXPERIMENTAL PART

Preparation of addition compounds. The olefin was mixed with bromotrichloromethane, and the mixture was illuminated in a glass vessel (Figure 2) containing a neon-type glass coil filled with mercury vapor. The vessel was equipped with a gas inlet tube, a sample tube, and a reflux condenser. Excess olefin and bromotrichloromethane were removed by

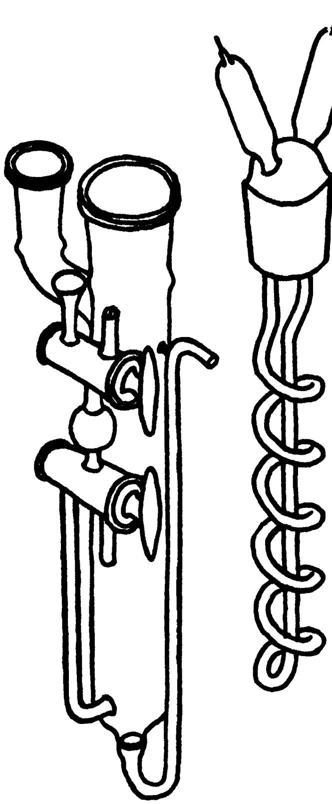


FIGURE 2

TABLE IV
ADDITION COMPOUNDS

OLEFIN	ADDITION COMPOUND (FORMULA)	B.P. °C AT 0.1 MM	n_D^{20}	SILVER EQUIVALENT	
				Calc'd	Found
Bicyclo[2.2.1]heptene-2	$C_8H_{10}BrCl_3$	70– 75	1.5538	73.1	73.2
Bicyclo[2.2.2]octene-2	$C_9H_{12}BrCl_3$	80– 85	1.5632	76.6	76.7
Cyclopentene	$C_6H_8BrCl_3$	30– 35	1.5331	66.6	66.6
Cyclohexene	$C_7H_{10}BrCl_3$	35– 40	1.5466	70.1	70.8
Dicyclopentadiene	$C_{11}H_{12}BrCl_3$	110–115	1.5753	82.6	82.3
Indene	$C_{10}H_8BrCl_3$	125–130	1.6001	78.6	79.1
Cyclopentadiene	$C_6H_6BrCl_3$	40– 45	1.5562	66.1	67.3
1,3-Cyclohexadiene	$C_7H_8BrCl_3$ (68%)	60– 65	1.5632	69.6	70.2
	$C_7H_8BrCl_3$ (32%)	60– 65	solid, m.p. 46°	69.6	68.9

distillation, and the residual addition compound was distilled at 0.1 mm. pressure. Table IV lists the addition compounds prepared.

Methods of competition analysis. A mixture containing 0.1 mole of each competing olefin

and 0.8 mole of bromotrichloromethane was illuminated in the apparatus hereafter described (Figure 2). The reaction was allowed to continue until about one-half of the available double bonds had reacted; this point was determined by bromide-bromate titration of samples removed from time to time. The excess bromotrichloromethane and olefins were removed by distillation, and the mixture of addition compounds was distilled at 0.1 mm. The composition of the mixture was determined by one or more of the following methods. (a) The two compounds were completely separated by distillation and the amount of each was determined gravimetrically. (b) The silver equivalent of the mixture was determined, and the quantity of each component was calculated. (c) A curve showing refractive index plotted against composition was prepared from the known mixture of the two pure addition compounds; the composition of the competition mixture was determined by the position of its refractive index on this curve. Whenever feasible all three of these methods were used. The feasibility of each method was in each instance determined by the difference between the boiling points, or the refractive indices or the silver equivalents of the two addition compounds in question.

Kinetic studies. Kinetic data were obtained by allowing 0.05 mole of the olefin to react with 0.4 mole of bromotrichloromethane in the internally irradiated apparatus hereafter described (Figure 2). The apparatus was immersed in a thermostated bath at the proper temperature. A slow stream of nitrogen was bubbled through the reaction mixture to stir it and to eliminate oxygen. A reflux condenser cooled with a mixture of carbon dioxide and acetone was used to prevent the loss of volatile olefins. The course of the reaction was followed by the bromide-bromate titration of samples withdrawn at regular intervals.

Dehydrohalogenation of addition compounds. 1-Trichloromethyl-3-bromocyclohexane (III) was heated with two molecular equivalents of sodium ethoxide in absolute ethanol for twenty-four hours at 20°. The reaction mixture was decomposed with water, and the aqueous solution was extracted with ether and benzene. The ether-benzene solution was dried, the solvent was removed, and the remaining oil was distilled at reduced pressure. A center cut was taken. The ultraviolet absorption spectrum of this material dissolved in isopropanol was determined with the aid of a Beckman type D spectrophotometer (see Figure 1). The product proved to be 3-dichloromethylenecyclohexene (IV).

Anal. Calc'd for $C_7H_8Cl_2$: Cl, 43.5. Found: Cl, 43.3, 43.1.

A portion (0.2 mole) either of the solid or the liquid addition compound obtained from 1,3-cyclohexadiene was treated for two hours at 50° with two molecular equivalents of 0.7 *N* alcoholic potassium hydroxide. The reaction mixture was first filtered to remove precipitated bromide and chloride and then added to water. The aqueous solution was extracted with ether and ligroin. The ether-ligroin solution was dried over sodium sulfate; after the solvent was removed the remaining oil was distilled at 0.1 mm. A center cut was taken. The ultraviolet absorption spectrum of this material dissolved in 2,2,4-trimethylpentane (isooctane) was determined with the aid of a Beckman type D spectrophotometer (see Figure 1). The product proved to be 3-dichloromethylene-6-hydroxycyclohexene (VIIa), n_D^{20} 1.5528.

Anal. Calc'd for $C_7H_8Cl_2O$: C, 47.0; H, 4.51; Cl, 39.6.
Found: C, 47.3, 47.9; H, 4.85, 5.21; Cl, 39.6, 39.2, 38.6.

Both the solid and liquid addition compounds of 1,3-cyclohexadiene were mixed with two molecular equivalents of sodium ethoxide in ethyl alcohol and allowed to stand at room temperature overnight. The precipitated salts were removed by filtration; the filtrate was diluted with water, and the aqueous solution was extracted with ligroin. The ligroin was dried over sodium sulfate; after the solvent had been removed, the remaining oil was distilled at 6 mm. pressure. The principal fraction (b.p. 78–80°, n_D^{20} 1.5336) is 3-dichloromethylene-6-ethoxycyclohexene (VIIb) containing about 25% of the 6-hydroxy compound (VIIa).

Anal. Calc'd for $C_9H_{12}Cl_2O$: C, 52.3; H, 5.81; Cl, 34.7.
Found: C, 50.95, 51.19; H, 5.83, 5.60; Cl, 36.7, 37.0, 36.4.

The ultraviolet absorption spectrum of this material dissolved in isooctane was determined with the aid of a Beckman type D spectrophotometer.

The addition compounds of bromotrichloromethane with bicyclo[2.2.1]heptene-2, (VIII) dicyclopentadiene (X) and bicyclo[2.2.2]octene-2 (IX) do not react when treated for 6 hours at 50° with 0.7 *N* potassium hydroxide in absolute ethanol.

Identification of bromotrichloromethane—indene addition product (2-trichloromethyl-3-bromoindane). Three grams of the addition compound was refluxed for 40 min. with 3.2 ml. of concentrated sulfuric acid and 2.5 ml. of water. The reaction mixture was diluted with water and ice, and extracted with benzene. The benzene extract was first washed with dilute alkali; then the alkaline solution was acidified. The white solid which precipitated at this point was crystallized from benzene; it melted at 234–235°. The value given in the literature for the melting point of indene-2-carboxylic acid is 234°. Indene-3-carboxylic acid melts at 161°.

Irradiation apparatus (Figure 2). The irradiation apparatus used in this work consisted of a reaction tube 30 mm. in diameter and approximately 200 mm. long. It had a standard taper 34/45 joint at the top and at the bottom a sintered disc through which gas was passed during the reaction. Through an outlet near the bottom of the reactor, 1-ml. samples were withdrawn by means of an arrangement of stopcocks and a 1-ml. bulb. A reflux condenser was attached to the apparatus by means of a 19/38 standard taper ground joint entering the reaction tube near the top. The lamp was fitted into the reactor tube by means of the 34/45 standard taper ground joint. This lamp was of the cold-electrode type with a filling of argon and mercury. The tubing of the coil was 6 mm. O.D. The lamp was operated from a 6000 volt, 20 milliampere transformer.

Acknowledgment. The authors wish to thank Dr. H. I. Pines of the Universal Oil Products Co. for the preparation of bicycloheptene and bicyclooctene by the high-pressure addition of ethylene to cyclopentadiene and cyclohexadiene, respectively. Mr. M. Sage prepared the dehydrohalogenate of the cyclohexene addition compound. The authors are also grateful to Mr. H. Jacobson for his aid in preparing some of the compounds used, and for carrying out most of the halogen analyses reported.

SUMMARY

1. The relative reactivities of cyclic olefins with respect to the addition of free trichloromethyl radicals have been studied. Compounds containing five-membered unsaturated rings are more reactive than the corresponding six-membered ring compounds.

2. The kinetics of the addition of bromotrichloromethane to olefins was studied.

3. The preparations of some conjugated cyclic olefin derivatives from bromotrichloromethane adducts are described.

CHICAGO 37, ILL.

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[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY, UNIVERSITY OF CHICAGO]

REACTIONS OF ATOMS AND FREE RADICALS IN SOLUTION. XX. THE ADDITION OF ALDEHYDES TO OLEFINS

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The photochemical additions of polyhalomethanes (1a), α-halogenated esters (1b), etc. (1c), to olefins, as well as the similar reactions induced by acyl peroxides have been described. The present paper deals with the preparation of ketones by the addition of aldehydes to 1-alkenes.

$$RCHO + R'CH{=}CH_2 \rightarrow RCOCH_2CH_2R' \qquad (A)$$

When a high ratio (6:1) of aldehyde to olefin is used, the principal products of the reaction are: (a) the one-to-one adduct (A), (b) small amounts of higher-boiling products (formed from two or more molecules of olefin to one molecule of aldehyde), (c) alkane derived from the alkyl radical of the aldehyde, and (d) carbon monoxide. The latter two products are formed in equimolecular amounts.

The structures of the ketones formed were established by analysis, by molecular weight determination and by comparison of the physical properties of the products with the physical properties of the same ketones prepared by conventional methods. In some instances, the identity of the ketones prepared by the new method and the ketones prepared by conventional methods was established by proving the identity of the respective hydantoin derivatives.

DISCUSSION

The products formed in the addition of aldehydes to olefins may be accounted for by the following series of reactions:

1. $RCHO + \underset{\text{from diacetyl peroxide}}{CH_3\cdot} \rightarrow CH_4 + \cdot C(R){=}O$ or $RCHO \xrightarrow{h\nu} \cdot C(R){=}O + H\cdot$
2. $\cdot C(R){=}O + R'CH{=}CH_2 \rightarrow \cdot CHR'CH_2COR$ (I)
3. $I + RCHO \rightarrow \cdot C(R){=}O + RCOCH_2CH_2R'$
4. $I + R'CH{=}CH_2 \rightarrow \cdot CHRCH_2CHR'CH_2COR$ (II)
5. $II + R'CH{=}CH_2 \rightarrow \cdot CHR'CH_2CHR'CH_2CHR'CH_2COR$ (III)

The formation of equimolecular quantities of an alkane and carbon monoxide is probably due to side reactions 6 and 7. Step 8 is the chain-terminating reaction, and in the addition of acetaldehyde to 1-octene the yield of biacetyl was about 30% that of the 2-decanone formed.

6. $\cdot C(R){=}O \rightarrow R\cdot + CO$
7. $R\cdot + RCHO \rightarrow RH + \cdot C(R){=}O$
8. $2\ \cdot C(R){=}O \rightarrow RCOCOR$

The non-formation of the one-to-one adducts of aldehydes and styrene is readily explained by the assumption that when R = C_6H_5, the activation energy required to enable the free radical (I) to remove a hydrogen atom from the aldehyde molecule is very high compared to the activation energy required for the addition of this free radical to another styrene molecule. Hence, reactions of the type indicated in steps 4 and 5 are favored, and the resulting products are, therefore, mixtures of polymers of high molecular weight. Bromotrichloromethane, on the other hand, adds readily to styrene at 50–60° to give a one-to-one adduct because at that temperature the free radical $\cdot CH(C_6H_5)CH_2CCl_3$ readily removes a bromine atom from bromotrichloromethane, thus propagating the chain.

A less complex reaction mixture is formed when the additions of aldehydes to olefins are initiated photochemically rather than by acyl peroxides. In the reactions induced by acyl peroxides the acid formed causes an aldol condensation of the aldehyde. Frequently, the aldol thus formed boils at about the same temperature as the ketonic product; this fact often makes the isolation of the ketone difficult. In the photochemical reaction, no acid is formed, and, hence, there is little or no aldol produced.

TABLE I

ADDITION OF ALDEHYDES TO OLEFINS

ALDEHYDE	OLEFIN	REACTION INITIATED BY	ADDITION PRODUCT	YIELD %
Ethanal	1-Octene	Ultraviolet light	2-Decanone	
Butanal	1-Octene	Ac_2O_2	4-Dodecanone	57
	1-Hexene	Ac_2O_2	4-Decanone	41
	Styrene	Ac_2O_2	Polymer	
	1-Octene	Visible light	4-Dodecanone	
2-Butenal	1-Octene	Ac_2O_2	Polymer	
Heptanal	1-Octene	Ac_2O_2	7-Pentadecanone	75
	1-Octene	Visible light	7-Pentadecanone	
	Cyclohexene	Visible light	1-Cyclohexyl-1-heptanone	

The best yields of ketones were obtained by adding long-chain aldehydes to long-chain 1-alkenes. Thus, the addition of ethanal to olefins gave low yields of methyl ketones. Similarly, butanal and heptanal when treated with propene gave low yields of propyl ketones. On the other hand, excellent yields of ketones were obtained when butanal or heptanal were added to 1-octene. Irrespective of the aldehyde used, cyclic olefins, such as cyclohexene, gave poor yields of ketones.

It is of interest that when a mixture of 2-butenal and 1-octene was either illuminated or heated in the presence of an acyl peroxide no one-to-one adduct was found; the reaction product consisted entirely of a high polymer. Furthermore, no carbon monoxide was liberated in this reaction. In this respect, 2-butenal resembles benzaldehyde which, unlike all saturated aliphatic aldehydes, gives no carbon monoxide when treated with acetyl peroxide. The non-formation of

carbon monoxide from these aldehydes is probably due to the high resonance energy of the free benzoyl and crotonyl radicals.

EXPERIMENTAL

Reagents. Heptanal, Eastman's, was first distilled through a 10-inch Vigreux column, dried over Drierite, and then distilled through a 50-plate Podbielniak column (b.p. 56°/23 mm.; n_D^{20} 1.4114).

1-Octene (Connecticut Hard Rubber Company) was distilled through a 50-plate column at atmospheric pressure (b.p. 118°; n_D^{20} 1.4090).

Eastman's butanal was first distilled through a 10-inch Vigreux column and dried over Drierite; it was then distilled through a 100-plate Podbielniak column (b.p. 74.2°; n_D^{20} 1.3819).

1-Hexene was distilled through the 50-plate column (b.p. 63.2°; n_D^{20} 1.3880).

Eastman's ethanal was distilled before use (b.p. 20°).

Cyclohexene was distilled through a 50-plate column (b.p. 82–83°; n_D^{20} 1.4454).

1-Bromohexane was prepared according to the directions of Kamm and Marvel (2). It was distilled through a 15-plate column packed with single-turn glass helices (b.p. 57°/28 mm.; n_D^{20} 1.4456).

1-Bromooctane was prepared in the same way. It was distilled through a 15-plate column (b.p. 40–41°/1 mm.; n_D^{20} 1.4528).

Styrene was distilled immediately before use (b.p. 144°; n_D^{20} 1.5460).

Eastman's 2-butenal was distilled through a 15-plate column (b.p. 102–103°; n_D^{20} 1.4375).

The peroxide-induced addition of heptanal to 1-octene. Acetyl peroxide (4.5 g.) dissolved in heptanal (14.2 g.) was dropped over a period of 9 hours into a solution containing 1-octene (31.4 g., 0.28 mole) and heptanal (114 g., 1.0 mole; b.p. 68°/40 mm.; n_D^{20} 1.4128) held at 65°. After the peroxide addition was complete, the reaction temperature (65°) was maintained for 10 hours. During the reaction period, a gas (7.1 liters N.T.P.; molecular weight, 26.3) was evolved. This gas was shown to be a mixture of methane (13%) and carbon monoxide (87%; 0.28 mole). The carbon monoxide content was determined by ammoniacal cuprous chloride absorption in a Moorhead apparatus.

The reaction mixture was distilled through a 50-plate Podbielniak column and the following fractions were collected: hexane (23.9 g.; n_D^{20} 1.3742; b.p. 63–68°; 0.28 mole); 1-octene (3.8 g.); heptanal (66.0 g.). The residue was distilled at reduced pressure through a 10-inch Vigreux column, and the fraction boiling at 63–70°/0.1 mm. (47.5 g.) was collected. This material crystallized upon standing. After two crystallizations from methanol, it melted at 32°. This substance was shown to be 7-pentadecanone.

Anal. Calc'd for $C_{15}H_{30}O$: C, 79.57; H, 13.36; Mol. wt., 226.

Found: C, 79.16; H, 13.22; Mol. wt., 236.

A residue (4.5 g.; mol. wt., 436) remained in the distilling flask.

Identification of the heptanal-1-octene addition product (7-pentadecanone). 7-Pentadecanol (34.7 g.) was prepared from *n*-octylmagnesium bromide (made from 1-bromooctane, 52 g., and magnesium, 7 g., in absolute ether, 180 ml.) and heptanal (23.0 g.; 0.20 mole) in 76% yield. The alcohol distilled at 95–100°/0.1 mm., and upon standing crystallized to a white solid. The solid melted at 36.5–38° after crystallization from methanol.

The 7-pentadecanol was oxidized with chromic anhydride in glacial acetic acid by the method of Karrer (3). The 7-pentadecanone isolated melted at 31–32° after two crystallizations from methanol. This material did not depress the melting point of the 7-pentadecanone obtained by the addition of heptanal to 1-octene.

The 7-pentadecanone was converted to its hydantoin derivative (4). After several crystallizations from 60% ethanol, the hydantoin (5-*n*-hexyl-5-*n*-octylhydantoin) melted at 121.5–122°.

Anal. Calc'd for $C_{17}H_{32}N_2O_2$: N, 9.45. Found: N, 9.24.

The hydantoin prepared from the product of addition of heptanal to 1-octene melted at 121–122°. It did not depress the melting point of the hydantoin derived from a known sample of 7-pentadecanone.

The peroxide-induced reaction of butanal with 1-octene. A mixture of butanal (42.9 g.; 0.596 mole) and 1-octene (18.1 g.; 0.162 mole) was held under reflux while a solution of acetyl peroxide (7.2 g.) in butanal (18.0 g.) was dropped in over a period of 3 hours. The reaction mixture was heated for 4 hours after the addition was complete.

The reaction mixture was distilled without further treatment. Unchanged butanal (b.p. 69–73°; 24.7 g.) distilled first. The residual reaction product was distilled at reduced pressure. A fraction was obtained (b.p. 65°/0.25 mm.; 17.2 g.; n_D^{20} 1.4313) which was shown to be 4-dodecanone. A residue (7.0 g.; n_D^{20} 1.4538) remaining in the distilling flask had an apparent molecular weight of 310.

The addition product of butanal to 1-octene was converted to the hydantoin. The hydantoin melted at 117–119° after three crystallizations from 60% ethanol.

Anal. Calc'd for $C_{14}H_{26}N_2O_2$: N, 11.01. Found: N, 11.22.

Identification of the butanal-1-octene addition product (4-dodecanone). 4-Dodecanone was prepared according to the general method outlined above for 7-pentadecanone. To *n*-octylmagnesium bromide, prepared from 1-bromooctane (52 g.; 0.27 mole) and magnesium (6.5 g.; 0.28 mole) in absolute ether (200 ml.), a solution of butanal (19.4 g.; 0.27 mole) in ether (50 ml.) was slowly added. Stirring of the reaction mixture was continued at room temperature for 24 hours.

The reaction mixture was treated with an aqueous acetic acid solution (30%), and the ether layer was washed with water and sodium carbonate solution (5%). The ether solution was dried over calcium sulfate. After the ether had been removed, the reaction product was distilled through a short Vigreux column. 4-Dodecanol (36.7 g.; n_D^{20} 1.4386; b.p. 76–78°/0.1 mm.) was obtained in 61% yield.

The 4-dodecanol was oxidized by the method of Karrer (3). The alcohol (20 g.; 0.11 mole) was treated with a solution containing chromic anhydride (10 g.), concentrated sulfuric acid (32 g.), and glacial acetic acid (100 g.). 4-Dodecanone (12.9 g.; n_D^{20} 1.4315; b.p. 71–73°/0.30 mm.) was obtained in 67% yield. These physical properties correspond with those of the addition product of butanal and 1-octene.

The 4-dodecanone prepared by the two methods was converted to 5-*n*-propyl-5-*n*-octylhydantoin. After one crystallization from 60% ethanol, both samples melted at 117–119°. The melting point of a mixture was not depressed.

The light-initiated reaction of ethanal with 1-octene. A solution containing ethanal (192.4 g.; 4.37 moles) and 1-octene (123.6 g.; 1.10 mole; b.p. 120°; n_D^{20} 1.4090) was placed in an irradiation tube fitted with a long quartz mercury resonance lamp. The apparatus was swept with nitrogen before use. The tube and its contents were cooled throughout the reaction by an ice-water bath. The reaction mixture was illuminated for 72 hours. During this time, gas (2000 ml.; methane, 47%; carbon monoxide, 51%) was evolved. The gas was passed through an ice-cooled condenser, a Dry Ice-acetone trap, and into a gas receiver.

Distillation at atmospheric pressure yielded: ethanal (185 g.); a small intermediate fraction (3 g.; b.p. 80–95°) containing biacetyl (diphenylhydrazone, m.p. 243°); 1-octene (115 g.). After these substances had been removed, the residue (18 g.) was distilled at reduced pressure. A fraction (7.5 g.; n_D^{20} 1.4267; b.p. 117°/37 mm.) was shown to 2-decanone by conversion to its semicarbazone (m.p. 124–125°) (5).

The distillation residue (10 g.) was a high-boiling material (molecular weight, 301).

The peroxide-induced addition of butanal to 1-hexene. A solution of acetyl peroxide (3.0 g.) in butanal (15.0 g.) was added dropwise over a period of 3 hours to a mixture of butanal (192.6 g.; 2.68 moles) and 1-hexene (60 g.; 0.71 mole) held at its boiling point. After the peroxide addition was completed, the reaction mixture was held under reflux for an additional 24 hours. During this period, it assumed a light-yellow color.

After residual butanal and 1-hexene had been distilled at atmospheric pressure, the reaction products were distilled at reduced pressure, and the following fractions were collected. Fraction I: 4.5 g., b.p. 60–92°/18 mm., n_D^{20} 1.4214. Fraction II: 15.4 g., b.p. 92–96.5°/18 mm., n_D^{20} 1.4253. Fraction III: 27.6 g., b.p. 96.5°/18 mm., n_D^{20} 1.4300. Residue: 15 g. Fractions II and III are presumably 4-decanone. However, the index of refraction of this material is somewhat higher than that of pure 4-decanone (n_D^{20} 1.4240) prepared by conven-

tional methods. It was suspected that the impurity in the 4-decanone was *n*-butyl butyrate, formed by reaction of acetyl peroxide with butanal (6). A determination of the saponification equivalent of Fraction III indicated about ten per cent of the ester. For this reason, Fraction III was converted to 5-propyl-5-hexylhydantoin. After two crystallizations from ethanol (60%) it melted at 117–119°.

Anal. Calc'd for $C_{12}H_{22}N_2O_2$: N, 12.38. Found: N, 12.03.

This hydantoin derivative did not depress the melting point of the hydantoin prepared from an authentic sample of 4-decanone.

The peroxide-induced addition of butanal to styrene. A solution of acetyl peroxide (3.0 g.) in butanal (7 g.) was added dropwise (over a period of seven hours) to a mixture of styrene (17.0 g.; 0.16 mole) and butanal (110 g.; 1.53 mole) at 90°. The reaction mixture was held at that temperature for one hour after the last addition of the peroxide.

The reaction mixture was distilled at reduced pressure through a 10-inch Vigreux column. After unchanged butanal (b.p. 38°/80 mm.) had distilled, the residue became viscous. A small fraction (3.0 g.; b.p. 30–32°/0.5 mm.; n_D^{20} 1.4160) distilled. The still-pot residue (14 g.) was a viscous polymeric product.

The peroxide-induced reaction of 2-butenal with 1-octene. A mixture of 1-octene (49 g.; 0.44 mole) and butenal (123 g.; 1.76 mole) was placed in a 250-ml. flask fitted through ground-glass joints with a dropping-funnel and a condenser. The apparatus was swept with dry carbon dioxide.

A solution of acetyl peroxide (4.5 g.) in butenal (23.4 g.) was slowly added over a period of 10 hours while the reaction mixture was held at 65–70°. After the peroxide solution had been added, heating was continued for 10 hours. A small amount of gas (250 ml.) was evolved during this time. It was shown to be almost pure methane (mol. wt., 16.5). A qualitative test for carbon monoxide was negative.

Unchanged butenal and 1-octene were removed from the reaction mixture by distillation (b.p. 40–70°/80 mm.). The residue (17 g.) was then distilled through a 10-inch Vigreux column. Only a small fraction (4.0 g.; b.p. 61–90°/0.1 mm.) distilled. The residue was a highly viscous syrup with an apparent molecular weight of 755.

Photochemical addition of heptanal to 1-octene. A mixture of 1-octene (29.0 g.; 0.26 mole) and heptanal (104.2 g.; 0.914 mole) was internally irradiated by a mercury vapor-neon fluorescent tube. The apparatus was thoroughly swept with nitrogen, and the light was turned on. The heat from the lamp maintained the reaction temperature at 70°. Illumination was continued for 23 hours. During that time 800 cc. of gas was evolved. The gas was passed through a trap immersed in a bath cooled by a mixture of Dry-Ice and acetone, and collected in gas reservoir.

The reaction mixture was distilled at atmospheric pressure and the following fractions were collected: Fraction I: hexane, 3 g.; Fraction II: 1-octene, 20 g.; Fraction III: heptanal, 90 g. The residue was distilled at reduced pressure, and the fraction (15 g.) boiling at 92°/2 mm. was collected. This fraction was 7-pentadecanone. It solidified upon standing. After crystallization from methanol, it melted at 31–32°. A residue (5 g.) remained in the distilling flask.

The photochemical addition of butanal to 1-octene. A mixture of butanal (109.5 g.; 1.52 mole) and 1-octene (33.0 g.; 0.295 mole) was illuminated internally by a mercury vapor-neon fluorescent tube. The reaction mixture was held at about 70° and illuminated for 26 hours. During this period, 2050 ml. of gas was collected. The gas was a mixture of 49% propane and 51% carbon monoxide.

The reaction mixture was distilled through a 50-plate Podbielniak column. The unchanged butanal (100 g.) and 1-octene (21 g.) were thus separated from the reaction product. The residue was distilled at reduced pressure through a 10-inch Vigreux column and the fraction boiling at 65°/0.2 mm. was collected. This material (n_D^{20} 1.4315) is 4-dodecanone. A residue (4 g.) remained in the distilling flask.

The photochemical addition of heptanal to cyclohexene. A mixture of heptanal (112.5 g.; 0.98 mole) and cyclohexene (22.0 g ; 0.27 mole) was irradiated internally by a mercury vapor-

neon fluorescent tube for 72 hours. During this time, 1650 ml. of gas was evolved. The gas consisted of 95% carbon monoxide.

Distillation of the reaction mixture yielded unchanged cyclohexene (15 g.) and heptanal (105 g.). A product, presumably 1-cyclohexyl-1-heptanone (10 g.; b.p. 73–80°/0.05 mm.; n_D^{20} 1.4486) was obtained.

SUMMARY

1. Ketones are formed by the addition of aldehydes to 1-alkenes. The reaction may be initiated photochemically or by acyl peroxides.

2. The following ketones have been prepared by the method indicated: 2-decanone, 4-decanone, 4-dodecanone, 7-pentadecanone, and 1-cyclohexyl-1-heptanone.

3. Polymers were obtained when mixtures of butanal and styrene, or 2-butenal and 1-octene were irradiated or treated with small quantities of acyl peroxides.

CHICAGO 37, ILL.

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[FROM THE DEPARTMENT OF CHEMISTRY OF THE POLYTECHNIC INSTITUTE OF BROOKLYN]

THE BECKMANN REARRANGEMENT OF ALIPHATIC KETOXIMES. A COMPARISON OF THE INFLUENCE OF REAGENTS ON THE COURSE OF THE REARRANGEMENT[1]

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As pointed out previously (1), Hantzsch (2) reports that two amides are obtained from the Beckmann rearrangement of methyl isopropyl ketoxime whereas Sidgwick (3) states that only one is obtained. The principal product from the oxime

$$CH_3C(=NOH)R \qquad \text{I}$$

was shown by Hantzsch to be

$$CH_3CONHR \qquad \text{II}$$

when R is ethyl, *n*-propyl, isopropyl, or *n*-hexyl. The same is true for $C_2H_5C(CH_3)_2CH_2C(=NOH)CH_3$ and $(CH_3)_3CCH(CH_3)C(=NOH)CH_3$ as was found by Drake *et al.* (4). A similar result is obtained for 2-alkylcyclohexanone oximes which bear a formal resemblance to I (5, 6, 7, 8). To clear up the discrepancy in the literature, to discover whether the conditions of rearrangement are influential in determining the course of the reaction, and to decide whether preferential rearrangement is primarily caused by steric or electronegativity effects of $CH_3(CH_2)_n$- compared to CH_3- or C_2H_5- in aliphatic ketoximes, a quantitative study of this rearrangement has been carried out on a number of compounds with phosphorus pentachloride in ether (Table I) and sulfuric acid (Table II) as reagents.

The yields were about eighty per cent or higher, as previously reported (4). In view of yields less than one hundred per cent it was necessary to establish that all of the amides were recovered for calculation of mole fractions of products. This point was substantiated as described under Experimental.

The first factor investigated was the influence of the nature of R (Table I). It was observed that the mole fraction of *n*-alkyl amine varies from 0.66 to 1.03 with perhaps an alternation of mole fraction with number of carbon atoms in the homologous series of R. On the other hand, as the bond angle within R varied from 0° (*n*-propyl) to 60° (cyclopropyl) to 109° (isopropyl), the mole fraction of RNH_2 increased from 0.66 to 0.88 to 1.03 (or unity). This may indicate a steric hindrance in the neighborhood of $-\overset{|}{C}=NOH$. The inductive effects of the groups, however, are in the same order. A Fisher-Hirschfelder model of methyl isopropyl ketoxime shows a small amount of restricted rotation of isopropyl about $-C(=NOH)-CH_3$ for the syn form of the oxime. Thus the course of the re-

[1] From the M.S. thesis of R. E. Schachat, 1948.

arrangement may be influenced by the ratio of the geometrical isomers of the parent oximes. This is probably also true of 2-alkylcyclohexanone oximes.

That the difference observed in the mole fractions of RNH_2 from methyl *n*-propyl and methyl cyclopropyl ketoximes is real is shown by application of the

$$t = \frac{\overline{X}_1 - \overline{X}_2}{\left(\frac{n_1 + n_2}{n_1 + n_2 - 2}\right)^{1/2}\left(\frac{\Sigma(X_1 - \overline{X}_1)^2 + \Sigma(X_2 - \overline{X}_2)^2}{n_1 n_2}\right)^{1/2}}$$

"t" test (9). The quantity t is derived as for any two sets of data of n_1 and n_2 observations. By referring to a table supplied by Rider (9), t is converted to P (| t |) known as the "level of significance." Generally, if one finds a "level of significance" greater than .05 it cannot be concluded that any difference between the two sets has been shown. As an illustration, if two sets of observations were compared in the above manner and P (| t |) = 0.06, we could say that the level of significance was 6% or that there are about 6 chances in 100 of observing a *greater* difference between the two sets of data, even if both sets consisted of observations made on the same or identical systems. In the above instance of methyl *n*-propyl ketoxime (giving a mole fraction $RNH_2 \cdot HCl$ equal to 0.66 ± 0.07) and methyl cyclopropyl ketoxime (giving a mole fraction $RNH_2 \cdot HCl$ equal to 0.88 ± 0.18) t = << .01, therefore we may conclude with reasonable certainty that the two oximes give distinctly different mole fractions of RNH_2.

To see whether or not an electronegativity effect (1, 3) of propyl as compared to ethyl could also be observed, ethyl *n*-propyl ketoxime was rearranged. Again the migration of nitrogen was predominantly toward the longer radical, the more electron-releasing group (10).

Whether methyl isopropyl ketoxime rearranges to give but one amide as stated by Sidgwick, or two amides as claimed by Hantzsch apparently depends upon conditions of the rearrangement. With phosphorus pentachloride in ether or with 85% sulfuric acid and heat only one product was formed. With 93% sulfuric acid nearly equal amounts of the two amides were produced. This reaction took place with much more violence than the reaction with 85% acid. The behavior of oximes with phosphorus pentachloride as catalyst is further shown to be qualitatively different from that with 93% sulfuric acid by comparison of the respective yields from ethyl *n*-propyl ketoxime, Tables I and II. One can propose that at room temperature preponderently one form of the oxime exists for rearrangement but that under the high temperature of comparatively violent reaction in sulfuric acid more nearly equal amounts of both forms of oximes or the corresponding sulfate esters are available for rearrangement. No further explanation for the results can be offered until a study has been made of the composition of the oximes themselves, *i.e.*, syn or anti, as a function of temperature and solvent composition.

Finally, it may be pointed out that steric reasons are not the whole story since the greater than 0.5 mole fraction of *n*-propylamine from ethyl propyl ketoxime is an indication that the electrical fields of ethyl and propyl are different (10).

EXPERIMENTAL

Rearrangements with phosphorus pentachloride in ether. The oximes, prepared from the corresponding ketones in the usual way (7), were rearranged with phosphorus pentachloride in ether as described by Drake *et al.* (4) or in sulfuric acid (8). With the first method,the ether was removed by distillation on a steam-bath and the residue of amides from 0.5–1.0

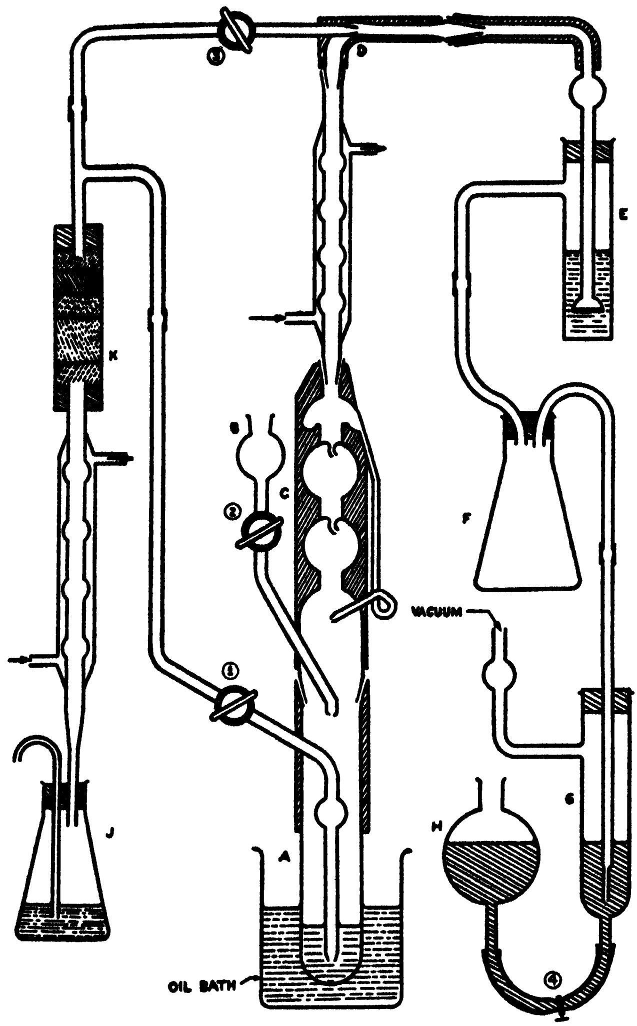

FIGURE 1. AMINE DISTILLATION APPARATUS

g. of oxime was poured onto 5–10 g. of ice in vessel A of the amine distillation apparatus (Fig. 1). This apparatus is an extensive modification of the ammonia entrainment apparatus of Lecoq (11). The transfer was made quantitative with the aid of boiling-water washings. After freezing the mixture of amides and washings, the apparatus was assembled as shown in Figure 1. Stopcocks "1" and "2", and screw clamp "4" were closed; stopcock "3" was left open. "E" contained 50 ml. of 2 N hydrochloric acid, "J" contained concentrated sulfuric acid, "G" and "H" contained mercury, "K" contained substances to remove

moisture and basic gases from the incoming air. A vacuum was applied to pressure regulator "G" so that a fine but steady stream of bubbles was drawn through the fritted glass disk on the inlet tube in "E". Incoming air entered the system by bubbling through the sulfuric acid of "J", then passed through absorption tube "K", through stopcock "3", through the dilute hydrochloric acid of "E", through trap and pressure-steadier "F", and finally through pressure regulator "G". With the air being drawn through the system as described above, 10 ml. of 10 N potassium hydroxide solution was cautiously added to "A" through funnel "B". The oil-bath was heated to 120–130° and maintained for two hours at this temperature producing gentle reflux. The amides in "A" were completely hydrolyzed by this treatment, causing amines to be released. The volatile amines passed through the reflux condenser, were caught in the air stream at point "D", and were dissolved in the hydrochloric acid at "E". The oil-bath was removed and the mixture allowed to cool for 10–15 min. without interruption of the air stream. Then, the condenser between "C" and "D" was removed and "D" was connected directly to "C". Stopcock "3" was closed, stopcock "1" was immediately opened, and the air flow was increased until it was two or three times its former rate. The oil-bath was replaced in its original position and heated to 190–220°, driving water and all amines into "E" where they were trapped. During this part of the process, vessel "E" was continuously cooled by a jet of cold water. About 5 minutes after dryness was reached in vessel "A", vessel "E" was removed from the system after which the vacuum was released.

The alkaline material in "A" was dissolved in a small quantity of water and extracted with chloroform. The chloroform solution was extracted with 2 N hydrochloric acid and the acidic solution was then combined with the distillate in "E". Evaporation from a weighed flask left a residue of amine hydrochlorides which were dried to constant weight. The chloride in the residue was converted to silver chloride according to Kolthoff and Sandell (12). The weight of silver chloride was used to compute the apparent molecular weight of the mixture of amine hydrochlorides as follows:

$$\text{app. mol. wt.} = \frac{143.34\,(\text{wt. of amine hydrochlorides})}{\text{weight silver chloride}}$$

From the apparent molecular weights of the amine hydrochloride mixtures, the absolute amounts of the two amines derived from the rearrangement were computed graphically by means of a molecular weight of amines versus mole fraction plot in the usual way. The results with known quantities of amides show that any carry-over of inorganic alkali into the chloroform was negligible or nil (see below).

Rearrangements with 93% sulfuric acid. About 0.5 g. of oxime was accurately weighed into a 125-ml. Erlenmeyer flask. One milliliter of 93% sulfuric acid was added. To prevent spattering, the flask was covered by a small funnel. The mixture was heated on a hot plate until a reaction had taken place, *i.e.*, about 110°. After cooling, the mixture was washed onto 5–10 g. of ice in receptacle "A" of the entrainment apparatus. Hydrolysis of the amides and distillation of the amines were performed as described above. Rearrangements with 85% sulfuric acid were performed in a similar manner.

Discussion of errors. (a) *Degree of rearrangement.* A sample of methyl *n*-propyl ketoxime was rearranged with phosphorus pentachloride in the usual manner. Instead of hydrolyzing the amides they were extracted with chloroform and weighed. The yield was 83.7% in excellent agreement with the results of Table I for this compound. That is, this method of rearrangement only produced an 84% yield; the fact that 16% of the material fails to rearrange cannot affect conclusions based on the results in Tables I and II. Aliphatic ketoximes apparently do not rearrange as completely with phosphorus pentachlorides in ether as with sulfuric acid (4, 5).

As shown with di-*n*-butyl ketoxime, any decomposition products from the rearrangement of unreacted ketoxime did not affect the molecular weight of the *n*-butylamine produced by more than 2%, Table I.

(b) *Stability of the cyclopropyl compounds.* A sample of methyl cyclopropyl ketoxime was rearranged and the resulting amides were hydrolyzed. The methylamine was allowed to escape while cyclopropylamine was retained and converted to its hydrochloride, m.p. 99° (13). In sulfuric acid rearrangements the cyclopropyl ring was destroyed.

(c) *Losses due to incomplete distillation of amines, incomplete hydrolysis, escape of amines from the hydrochloric acid solution, non-quantitative transfers, volatilization of the amine hydrochloride while drying, etc.* A series of compounds was used to assay the method, Table III. The explanation of the Table is as follows.

TABLE I

BECKMANN REARRANGEMENT OF KETOXIMES WITH PCl_5

KETOXIME	YIELD OF PRODUCTS, AVERAGE %	MOLE FRACTION[a] $RNH_2 \cdot HCl$[b]	NUMBER OF DETERMINATIONS
Methyl ethyl	81.0	0.73 ± 0.06	4
Methyl *n*-propyl	83.6	0.66 ± 0.07	6
Methyl isopropyl	83.0	1.03 ± 0.00	2
Methyl cyclopropyl	80.1	0.88 ± 0.18	7
Methyl *n*-butyl	73.6	0.79 ± 0.13	7
Methyl *n*-amyl	75.9	0.68 ± 0.23	6
Methyl *n*-hexyl	72.8	0.69 ± 0.03	4
Ethyl *n*-propyl	73.7	0.85 ± 0.18	6
Di-*n*-butyl	40.2	0.98	1

[a] Mole fractions are given as plus or minus 2σ where

$$\sigma = \sqrt{\frac{\Sigma\,(X - \overline{X})^2}{n}}\;\sqrt{\frac{n}{n-1}}$$

and n is the number of determinations; $(\overline{X} - \overline{X})$ is the difference between individual values, X, and the mean, $\overline{X}$.

[b] R = longer chain.

TABLE II

BECKMANN REARRANGEMENT OF KETOXIMES WITH 93% H_2SO_4

KETOXIME	YIELD OF PRODUCTS, AVERAGE %	MOLE FRACTION OF $RNH_2 \cdot HCl$	NUMBER OF DETERMINATIONS
Methyl *n*-propyl	87.6	0.79 ± 0.05	3
Methyl isopropyl	87.8	0.57 ± 0.06	5
Ethyl *n*-propyl	92.3	0.58 ± 0.05	3
Methyl isopropyl[a]	85.5	1.01 ± 0.18	2

[a] Rearrangement with 85% sulfuric acid.

A weighed amount of *n*-amylamine hydrochloride was inserted into vessel "A" of the apparatus, an excess of potassium hydroxide solution was added, and 99.4% of the amine was recovered upon distillation and reconversion to the hydrochloride (Exp. 1). Weighed amounts of known amides were hydrolyzed and then distilled. The recovery was about 96% (Exps. 2, 3, 4). Weighed amounts of two different amides were placed in the apparatus, hydrolyzed and distilled. The recovery was about 93% and the experimental percentages of amines agreed closely with the expected (Exps. 5, 6, 7).

SUMMARY

A series of aliphatic ketoximes were rearranged and the mole fractions of the resulting amides were determined.

In all cases the rearrangement favored the formation of amides of the form R^1CONHR where R is longer than R^1. The relative proportion of the favored form increased in the order R = *n*-propyl, cyclopropyl, isopropyl, with phosphorus pentachloride in ether as catalyst.

TABLE III

STANDARDIZATION OF THE EQUIPMENT

EXP. NO.	COMPOUND USED	RESULTS
1	*n*-Amylamine hydrochloride	M.W. (theo.): 123.6; M.W. (exp.): 124.6. Recovery: 99.4%
2	N-Ethyl acetamide	M.W. (theo.): 81.5; M.W. (exp.): 83.8. Recovery: 96.0%
3	N-Ethyl acetamide	M.W. (theo.): 81.5; M.W. (exp.): 83.0. Recovery: 96.6%
4	N-*n*-Amyl acetamide	M.W. (theo.): 123.6; M.W. (exp.): 120.1. Recovery: 95.7%
5	N-Ethyl acetamide and N-*n*-Amyl acetamide	% Ethylamine (theo.): 52.0% % Ethylamine (exp.): 49.6% Total Recovery: 92.8%
6	N-Ethyl acetamide and N-*n*-Amyl acetamide	% Ethylamine (theo.): 72.2% % Ethylamine (exp.): 72.6% Total Recovery: 93.7%
7	N-Ethyl acetamide and N-*n*-Amyl acetamide	% Ethylamine (theo.): 58.9% % Ethylamine (exp.): 56.8% Total Recovery: 91.6%

The mole fractions of amides obtained from aliphatic ketoximes was different with phosphorus pentachloride than with 93% sulfuric acid.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF DUKE UNIVERSITY]

1,2 AND 1,4 ADDITIONS OF CINNAMIC ACID DERIVATIVES WITH SODIO KETONES, GRIGNARD REAGENTS, AND METALLIC AMIDES

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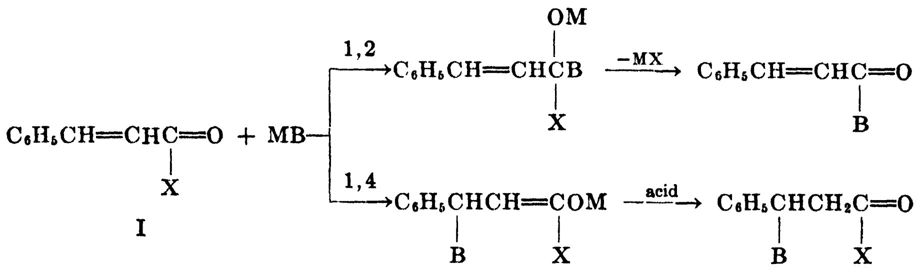
Cinnamic acid derivatives (I) might exhibit with sodio ketones, Grignard reagents, and metallic amides either 1,2 or 1,4 addition. These two courses of reaction may be illustrated by the following general scheme in which MB represents the basic reagent.



In the present investigation a study has been made of the relative extents of these two courses of reaction with certain of these basic reagents as X in (I) is varied. Although the magnesium of Grignard reagents (and perhaps also the sodium of sodio ketones) may first coordinate with the carbonyl oxygen of (I), the relative extents of formation of the 1,2 and 1,4 addition products are assumed to be dependent on the relative rates of addition of the basic anions at the carbonyl carbon and β-carbon, respectively. Because X is in closer proximity to the carbonyl carbon than to the β-carbon, its electronic and steric effects should influence the rate of the 1,2 addition more than that of the 1,4 addition. Consequently, a variation in X which would decrease the rate of the 1,2 addition should increase the relative extent of the 1,4 addition. The relative rate of the 1,2 addition might be expected to decrease as X is varied in the order, Cl, OC_6H_5, OCH_3 or OC_2H_5, $OC(CH_3)_3$, $N(C_2H_5)_2$, since, with the corresponding acetic or benzoic acid derivatives, this is known to be the decreasing order of the relative ease of alkaline hydrolysis, which may be considered to involve 1,2 addition with sodium hydroxide. Therefore, cinnamic acid derivatives (I) might be expected to exhibit, with a particular basic reagent, relatively less 1,2 addition and relatively more 1,4 addition as X is varied in this order. In general, this expectation has been realized. This can be seen from the results summarized in Table I which are taken from the present investigation and from the literature. Thus with sodio acetophenone, 1,2 addition occurs when X is chlorine and apparently mainly when X is phenoxy whereas 1,4 addition takes place mainly when X is

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methoxy or ethoxy; with phenylmagnesium bromide, 1,2 and 1,4 addition appear to occur to about equal extents when X is phenoxy whereas 1,4 addition is realized largely when X is ethoxy and exclusively when X is *t*-butoxy or diethylamino; with sodium amide, 1,2 addition predominates when X is ethoxy or *t*-butoxy whereas 1,4 addition occurs partly when X is diethylamino; with diethylaminomagnesium bromide, 1,2 addition occurs mainly when X is methoxy whereas 1,4 addition is realized when X is *t*-butoxy. The basis for these generalizations and also certain related reactions are discussed below.

Reactions with sodio ketones. Ryan and Dunlea (1) reported that sodio acetophenone, prepared by means of sodium amide, or sodio acetone, prepared by means of metallic sodium, reacted with ethyl or methyl cinnamate by 1,2 addition to form the corresponding β-diketone. However, in each case the yield was only about 6%. Stobbe (2) reported, that in the presence of sodium ethoxide,

TABLE I

MODE OF ADDITION OF BASIC REAGENTS TO $C_6H_5CH{=}CHCOX$ AS X IS VARIED

REAGENT	CL	OC_6H_5	(OCH_3) OC_2H_5	$OC(CH_3)_3$	$N(C_2H_5)_2$
$Na(CH_2COC_6H_5)$	1,2	1,2 (1,4?)[a]	1,4 (1,2)[a]		
C_6H_5MgBr	1,2 and 1,4?	1,2 and 1,4	1,4 (1,2)[a]	1,4	1,4
$NaNH_2$			1,2	1,2	1,4 (1,2)[a]
$(C_2H_5)_2NMgBr$			1,2 (1,4?)	1,4	

[a] Realized to a relatively small extent.

acetophenone added to ethyl cinnamate by 1,4 addition to form the Michael condensation product but no yield was given.

In the present investigation, it was found that sodio acetophenone, prepared by means of sodium amide, reacted with methyl or ethyl cinnamate by 1,4 addition to form the Michael condensation product which, on hydrolysis, gave β-phenyl-γ-benzoylbutyric acid (II) in 49% and 66% yield, respectively. Similarly, sodio pinacolone reacted with ethyl cinnamate to give the Michael condensation product in 64% yield. None of the β-diketone which would result from 1,2 addition was found; however, the copper salt method for the isolation of the β-diketone, used by Ryan and Dunlea, was not employed. The main reaction with ethyl cinnamate and sodio acetophenone may be represented as

$$C_6H_5CH{=}CHCO_2C_2H_5 + Na(CH_2COC_6H_5) \rightarrow \left[\begin{array}{c} C_6H_5CHCHCO_2C_2H_5 \\ | \\ CH_2COC_6H_5 \end{array}\right] Na \xrightarrow{+\text{ acid}}$$

$$\begin{array}{c} C_6H_5CHCH_2CO_2C_2H_5 \\ | \\ CH_2COC_6H_5 \end{array} \xrightarrow[(NaOH)]{HOH} \begin{array}{c} C_6H_5CHCH_2CO_2H \\ | \\ CH_2COC_6H_5 \\ \text{II} \end{array}$$

The yields reported above were obtained using a slight excess (10%) of the sodio ketone. When one molecular equivalent of ethyl cinnamate to one equivalent each of sodio acetophenone and sodium amide was used, the yield of II was lower (37%). The reaction was realized also with a catalytic amount (10 mole %) of sodium amide but the yield was only 19%.

When phenyl cinnamate, in which the carbonyl group is more reactive, sodio acetophenone and sodio acetone reacted by 1,2 addition to give the corresponding β-diketone in yields of 29–30%. Since these reactions were carried out with one molecular equivalent each of the ester and sodio ketone in the presence of an equivalent of sodium amide, the β-diketone was converted to its sodium derivative presumably by the sodium amide (3). The formation of cinnamoylacetophenone (III) may be represented as

$$C_6H_5CH{=}CHCO_2C_6H_5 \xrightarrow[NaNH_2]{NaCH_2COC_6H_5}$$

$$[C_6H_5CH{=}CHCOCHCOC_6H_5]Na \xrightarrow{acid} \underset{\text{III}}{C_6H_5CH{=}CHCOCH_2COC_6H_5}$$

In addition to the β-diketone, there was obtained a considerable quantity of a viscous red oil from which nothing could be crystallized. On refluxing the oil with sodium hydroxide, a small amount (3%) of an acid was obtained which appeared to be β-phenyl-γ-benzoylbutyric acid, presumably resulting from 1,4 addition.

When the reaction was carried out using two equivalents of sodio acetophenone to one of phenyl cinnamate, the yield was considerably lower (15%). In this case, a small amount of white solid was obtained in addition to the yellow cinnamoylacetophenone. The white compound was evidently compound IV, which was formed apparently from both a 1,2 and a 1,4 addition; it has not been established which mode of addition occurred first.

$$\begin{array}{l} C_6H_5CHCH_2COCH_2COC_6H_5 \\ \quad\;| \\ \quad CH_2COC_6H_5 \end{array}$$

IV

As was expected, cinnamoyl chloride underwent 1,2 addition with sodio acetophenone to form the sodium salt of III which was acylated in the reaction mixture to give dicinnamoylacetophenone (V) in 66% yield.

$$C_6H_5CH{=}CHCOCl \xrightarrow{NaCH_2COC_6H_5} C_6H_5CH{=}CHCOCH_2COC_6H_5 \xrightarrow{NaCH_2COC_6H_5}$$

$$[C_6H_5CH{=}CHCOCHCOC_6H_5]Na \xrightarrow{C_6H_5CH{=}CHCOCl} \underset{\text{V}}{(C_6H_5CH{=}CHCO)_2CHCOC_6H_5}$$

The product was shown to be a diacyl derivative rather than a 1,4 addition compound, by synthesis from sodio cinnamoylacetophenone (the sodium salt of III) and cinnamoyl chloride. That it was the C-acyl derivative (V) rather than the O-acyl derivative was indicated by its formation of a copper salt from which it was regenerated.

Reactions with Grignard reagents. Kohler and co-workers (4) have shown that, with phenylmagnesium bromide, ethyl cinnamate exhibits mainly 1,4 addition to form the ester of β,β-diphenylpropionic acid (VII). Some ($<$ 10%) 1,2 addition also occurs under certain conditions to form benzalacetophenone which undergoes 1,4 addition with the Grignard reagent in the reaction mixture to give β,β-diphenylpropiophenone (VI). With methyl cinnamate (4), relatively more 1,2 addition was realized while with phenyl cinnamate (5) almost equal amounts of 1,2 and 1,4 addition were observed. The two courses of reaction with phenyl cinnamate may be represented as

$$C_6H_5CH{=}CHCO_2C_6H_5 \xrightarrow[1,2]{C_6H_5MgBr} C_6H_5CH{=}CHCOC_6H_5 \xrightarrow[1,4]{C_6H_5MgBr} \underset{\text{VI}}{(C_6H_5)_2CHCH_2COC_6H_5}$$

$$C_6H_5CH{=}CHCO_2C_6H_5 \xrightarrow[1,4]{C_6H_5MgBr} (C_6H_5)_2\dot{C}HCH_2CO_2C_6H_5 \xrightarrow{HOH} \underset{\text{VII}}{(C_6H_5)_2CHCH_2CO_2H}$$

Kohler reported that with *n*-amyl cinnamate (4), less 1,2 addition was observed than with ethyl cinnamate but no yields were given. It has been shown in this laboratory (6) that phenylmagnesium bromide gives apparently only 1,4 addition with *t*-butyl cinnamate, which has a relatively unreactive ester group. In the present work, this has been confirmed the yield being increased from 44% to 76%.

$$C_6H_5CH{=}CHCO_2C(CH_3)_3 \xrightarrow{C_6H_5MgBr} (C_6H_5)_2CHCH_2CO_2C(CH_3)_3$$

Maxim (7, 8) has shown that di-substituted cinnamic amides, for example, N,N-diethyl cinnamamide, gave excellent yields of 1,4 addition product.

$$C_6H_5CH{=}CHCON(C_2H_5)_2 \xrightarrow{C_6H_5MgBr} (C_6H_5)_2CHCH_2CON(C_2H_5)_2$$

The course of addition of phenylmagnesium bromide to cinnamoyl chloride has been difficult to determine. Kohler concluded that both 1,2 and 1,4 addition occurred but he gave no yields. There is no doubt that he realized 1,2 addition since he isolated β,β-diphenylpropiophenone (VI) after treatment of the reaction product with alcoholic potassium hydroxide. He represented the reaction as taking place thus (4)

$$C_6H_5CH{=}CHCOCl \xrightarrow{C_6H_5MgBr} C_6H_5CH{=}CHCOC_6H_5 \xrightarrow{C_6H_5MgBr}$$

$$(C_6H_5)_2CHCH{=}\overset{\overset{\large OMgBr}{|}}{C}C_6H_5 \xrightarrow{C_6H_5CH=CHCOCl}$$

$$\underset{\text{VIII}}{(C_6H_5)_2CHCH{=}\overset{\overset{\large OOCCH=CHC_6H_5}{|}}{C}C_6H_5} \xrightarrow[\text{KOH}]{\text{alc}} \text{VI}$$

β,β-Diphenylpropionic acid (VII) also was isolated after hydrolysis. Kohler considered that this acid resulted from direct 1,4 addition of the Grignard reagent to the acid chloride but it might have arisen from 1,4 addition of the reagent to compound VIII which Kohler assumed to be formed from 1,2 addition as represented above. In an experiment with phenylmagnesium bromide and a large excess of cinnamoyl chloride, we isolated only a 1% yield of acid VII. A mixture that was difficult to separate was obtained as the main product; it was not further studied. In this connection it should be pointed out that Nightingale and Wadsworth (9) have shown that cinnamoyl chloride exhibits 1,2 addition with diphenylcadmium to form benzalacetophenone. We have found that diphenylcadmium fails to react with ethyl cinnamate in refluxing ether or benzene, 90% of the ester being recovered unchanged.

In contrast to phenylmagnesium bromide, methylmagnesium iodide appears to give 1,2 addition exclusively; however, the yields have been low. Kohler (4) reported a 27% yield of benzalacetone from methyl cinnamate while Maxim (8) obtained a poor yield of this ketone from N-methyl cinnamanilide. We have been unable to realize appreciable 1,4 addition with methylmagnesium iodide and *t*-butyl cinnamate or N,N-diethyl cinnamamide and with *t*-butylmagnesium chloride and methyl cinnamate. No attempt was made to isolate the 1,2 addition product.

Maxim (7, 8) realized 1,4 addition of ethylmagnesium bromide to di-substituted cinnamamides in excellent yields. However, we have been unable to realize appreciable 1,4 addition with this Grignard reagent and *t*-butyl cinnamate.

Reactions with amino bases. Although cinnamoyl chloride has been reacted with ammonia and various amines, and ethyl cinnamate with ammonia (10, 11) methylamine (11b) and diethylamine (11b), reactions of cinnamic acid derivatives with sodium amide or sodium or magnesium derivatives of amines have apparently not previously been reported.

In the present investigation, sodium amide in liquid ammonia was found to react readily with ethyl cinnamate and even with *t*-butyl cinnamate, by 1,2 addition, to give cinnamamide in 76% and 62% yields, respectively.

$$C_6H_5CH{=}CHCO_2R \xrightarrow{NaNH_2} C_6H_5CH{=}CHCONH_2$$

However, sodium amide reacted with N,N-diethyl cinnamamide to give a 17% yield of the 1,4 addition compound, N,N-diethyl β-aminohydrocinnamamide (IX), a small amount ($<$ 1%) of cinnamamide, and a considerable quantity of a high-boiling unidentified liquid. The reaction mixture immediately assumed a bright red color which changed within one minute to a deep purple. None of the N,N-diethyl cinnamamide was recovered.

$$C_6H_5CH{=}CHCON(C_2H_5)_2 \xrightarrow{NaNH_2} \underset{\displaystyle NH_2}{C_6H_5\overset{}{C}H}CH_2CON(C_2H_5)_2$$

IX

Sodioaniline, anilinomagnesium bromide, and isobutylaminomagnesium bromide reacted with *t*-butyl cinnamate by 1,2 addition to form the corresponding substituted cinnamamides in yields of 60%, 36%, and 30%, respectively. In the latter two cases, unchanged *t*-butyl cinnamate was recovered in yields of 40% and 43%, respectively. Also, sodiomethylaniline reacted with *t*-butyl cinnamate to give the 1,2 addition product, N-methyl cinnamanilide, in 54% yield. The reaction with the anilino bases may be represented as

$$C_6H_5CH{=}CHCO_2C(CH_3)_3 \xrightarrow[BrMgNHC_6H_5]{NaNHC_6H_5 \text{ or}} C_6H_5CH{=}CHCONHC_6H_5$$

However, diethylaminomagnesium bromide reacted with *t*-butyl cinnamate apparently by 1,4 addition, the primary product reacting further by a Michael type condensation to form (X) in 21% yield; unchanged *t*-butyl cinnamate (33%) was recovered.

$$C_6H_5CH{=}CHCO_2C(CH_3)_3 \xrightarrow{(C_2H_5)_2NMgBr}$$

$$\begin{array}{l} \qquad\qquad\quad OMgBr \\ \qquad\qquad\quad\ | \\ C_6H_5CHCH{=}COC(CH_3)_3 \\ \quad\ | \\ N(C_2H_5)_2 \end{array} \xrightarrow[+\text{ acid}]{C_6H_5CH{=}CHCO_2C(CH_3)_3} \begin{array}{l} C_6H_5CHCH_2CO_2C(CH_3)_3 \\ \quad\ | \\ \quad CHCO_2C(CH_3)_3 \\ \quad\ | \\ C_6H_5CHN(C_2H_5)_2 \\ \qquad\qquad \text{X} \end{array}$$

With methyl cinnamate, diethylaminomagnesium bromide reacted by 1,2 addition to give N,N-diethyl cinnamamide in 25% yield.

$$C_6H_5CH{=}CHCO_2CH_3 \xrightarrow{(C_2H_5)_2NMgBr} C_6H_5CH{=}CHCON(C_2H_5)_2$$

In addition methyl cinnamate (28%) was recovered, and there was isolated a product which appeared to be N,N-diethyl β-diethylaminohydrocinnamamide (XI) (11%), resulting from both 1,2 and 1,4 addition. Since N,N-diethylcinnamamide failed to add diethylaminomagnesium bromide under similar conditions, compound XI appears to have resulted from 1,4 addition followed by 1,2 addition.

$$\begin{array}{l} C_6H_5CHCH_2CON(C_2H_5)_2 \\ \qquad\ | \\ \qquad N(C_2H_5)_2 \\ \qquad\quad \text{XI} \end{array}$$

EXPERIMENTAL[2]

Phenyl cinnamate was prepared from cinnamoyl chloride and phenol by a modification of the general method of preparation of phenyl esters (12), using dimethylaniline in place of pyridine and carbon tetrachloride as solvent. A 74% yield of the ester, m.p. 70–71°, was obtained. After further recrystallizations the ester melted at 75–76° (13); yield, 35%.

t-Butyl cinnamate was prepared from *t*-butyl alcohol and cinnamoyl chloride in the presence of dimethylaniline (14). Since the ester appeared to be contaminated with

[2] Melting points are corrected; boiling points are uncorrected. Microanalyses are by Oakwold Laboratories, Alexandria, Virginia.

cinnamoyl chloride, an ether solution of the product was washed twice with 10% sodium hydroxide. The ether solution was dried over Drierite and the solvent distilled. Fractionation of the residue yielded pure ester (54%), b.p. 122.5–123.5° at 3 mm.

N,N-Diethyl cinnamamide was prepared by a modification of the method of Maxim (15). Cinnamoyl chloride, prepared from 0.6 mole each of cinnamic acid and thionyl chloride, was dissolved in 300 ml. of ether. This solution was added to 87.6 g. (1.2 mole) of diethylamine (b.p. 55.5–56.5°) in 300 ml. of ether in an ice-bath. Water (500 ml.) was added and the ether layer was washed several times with 10% sulfuric acid, then with saturated sodium bicarbonate solution and was finally dried over Drierite. The solvent was distilled and the residue recrystallized from ligroin (70–90°) yielding 101 g. (83%) of colorless needles, m.p. 68–69°. Vorlander and Herrmann (16) report the m.p. as 66° and, Cromwell and Caughlan (17), as 72°. The latter workers describe a good general procedure for the preparation of cinnamamides from cinnamoyl chloride and various secondary amines.

Condensations of ketones with cinnamic acid esters. The ketones were first converted to sodio ketones by means of sodium amide suspended in ether (3). Conversion was assumed to be complete within five to ten minutes. The ester was added to the sodio ketone at room temperature and the resulting mixture was refluxed for one hour. The reaction mixture from phenyl cinnamate and acetone was poured into water and the cinnamoylacetone was precipitated from the aqueous phase with carbon dioxide. In all other cases the reaction mixture was poured onto a mixture of ice and a slight excess of acetic or hydrochloric acid. The ether phase was washed with saturated sodium bicarbonate solution dried over Drierite, and the solvent distilled. The residue from the reaction of ethyl or methyl cinnamate was either fractionated and the direct Michael condensation product isolated or it was hydrolyzed with 10% sodium hydroxide to the acid which was isolated. The residue from the reaction of phenyl cinnamate with acetophenone was dissolved in a minimum amount of methanol and chilled; cinnamoylacetophenone precipitated and was filtered off. The methanol was evaporated from the filtrate and an attempt was made to distill the resulting oil; however, only phenol distilled. The oil remaining in the distilling flask was then refluxed with 10% sodium hydroxide for two and one-half hours yielding 0.38 g. (3%) of an acid, m.p. 146–148° which appeared to be slightly impure β-phenyl-γ-benzoylbutyric acid. Stobbe (2) reported the melting point to be 152–153.5°; in this investigation it was found to be 156–157°.

When the reaction of one equivalent of phenyl cinnamate with two equivalents of sodioacetophenone was carried out, there was obtained from the methanol filtrate a small amount of a white compound which, after recrystallization from alcohol and water, melted at 89–90°. Microanalysis indicated that it was 1,5-dibenzoyl-4-phenylpentanone-2.

Anal. Calc'd for $C_{25}H_{22}O_3$: C, 81.06; H, 5.99.
Found: C, 81.39; H, 5.91.

In each case, some cinnamic acid (5–15%) was obtained on acidification of the sodium bicarbonate wash solution except in the reaction of ethyl cinnamate with pinacolone; here β-phenyl-γ-pivaloylbutyric acid (3%), presumably resulting from hydrolysis of the 1,4 addition product, was obtained.

The yields of the main products using various proportions of the reactants are given in Table II.

Condensation of acetophenone with cinnamoyl chloride. Sodioacetophenone (0.1 mole) was prepared in 180 ml. of ether and dry nitrogen was passed through the suspension while refluxing for one hour to insure complete removal of the ammonia. The ether suspension of the sodio ketone was chilled in a Dry Ice-ether bath (−70°) and cinnamoyl chloride (approximately 0.1 mole, prepared from 14.8 g. of cinnamic acid and 19 ml. of thionyl chloride) dissolved in 75 ml. of ether was added. The resulting yellow suspension was stirred at room temperature for one hour and poured into ice-water containing 5 ml. of glacial acetic acid. A yellow solid separated and was filtered off. The ether phase was dried over Drierite and, after distillation of the solvent, more yellow solid was obtained. The combined product was washed with boiling methanol and dried, yielding 12.5 g. (66%) of dicinnamoyl-

acetophenone, m.p. 181–183°. Two recrystallizations from methanol gave material, m.p. 189–190°.

Anal. Calc'd for $C_{26}H_{20}O_3$: C, 82.08; H, 5.30.
Found: C, 81.62; H, 5.62.

The molecular weight was determined by the freezing point method in benzene; Calc'd for $C_{26}H_{20}O_3$: 380. Found: 382.

The product was further identified by the mixed melting point method using a sample synthesized by reacting equivalent amounts of cinnamoyl chloride with the sodium derivative of cinnamoylacetophenone prepared by means of sodium amide in ether suspension. After refluxing for thirty minutes on the steam-bath, the reaction mixture was poured into water containing acetic acid. The ether phase was washed with water, dried over Drierite and the solvent distilled. The residue was boiled with methanol and filtered giving dicinnamoylacetophenone, m.p. 186–187°, in 40% yield; unreacted cinnamoylacetophenone (26%) was recovered from the methanol filtrate.

TABLE II

CONDENSATIONS OF KETONES WITH CINNAMIC ACID ESTERS

CINNAMIC ESTER	MOLES	KETONE	MOLES	SODIUM AMIDE (MOLES)	PRODUCT	M.P., °C.	YIELD, %
Ethyl cinnamate	0.1	Acetophenone	0.11	0.11	β-Phenyl-γ-benzoyl-butyric-acid	156–157[a]	66
Ethyl cinnamate	0.1	Acetophenone	0.1	0.2	β-Phenyl-γ-benzoyl-butyric-acid	156–157[a]	37
Ethyl cinnamate	0.1	Acetophenone	0.1	0.01	Ethyl β-phenyl-γ-benzoyl butyrate[b]	61.0–61.5[c, d]	19
Methyl cinnamate	0.1	Acetophenone	0.11	0.11	β-Phenyl-γ-benzoyl-butyric acid	156–157[a]	49
Ethyl cinnamate	0.1	Pinacolone	0.11	0.11	Ethyl β-phenyl-γ-pivaloyl[e] butyrate	b.p. 169–171/5 mm.	64
Phenyl cinnamate	0.05	Acetophenone	0.05	0.1	Cinnamoylacetophenone	108.5–109.5[f]	29
Phenyl cinnamate	0.05	Acetophenone	0.1	0.1	Cinnamoylacetophenone	108.5–109.5[f]	15
Phenyl cinnamate	0.05	Acetone	0.05	0.1	Cinnamoylacetone	83–84[g]	30

[a] Literature (2); 152–153.5°. The oxime melted at 145.5–146.5°; literature (2); 144–144.5°.

[b] Hydrolysis of a sample of the ester gave the acid, m.p. 156–157°.

[c] Literature (19): 59–61°.

[d] B.p. 221–231°/5 mm.

[e] Hydrolysis of a sample of the ester gave the acid, m.p. 124–125°; literature (20): 124°. The amide melted at 132–133°; literature (20): 133°.

[f] Literature (1): 109°.

[g] Literature (1): 83–84°.

The dicinnamoylacetopenone in methanol solution formed a copper derivative (m.p. 247–249°) on treatment with excess saturated copper acetate solution; it was largely recovered on shaking the copper derivative with 20% sulfuric acid.

Reactions of Grignard reagents with cinnamic acid derivatives. To phenylmagnesium bromide, prepared from 5.1 g. (0.21 g. atom) of magnesium and 33 g (0.21 mole) of bromobenzene (b.p. 157°) in 95 ml. of ether, was added 35 g. (0.172 mole) of *t*-butyl cinnamate, fol-

lowed by refluxing on the steam-bath for four hours essentially as described previously (6). A thick yellow precipitate separated. In contrast to the earlier experiment, the reaction mixture was decomposed with ice cold 10% sulfuric acid. The ether phase was washed with saturated sodium bicarbonate and dried over Drierite. The solvent was distilled and the residue steam distilled to remove biphenyl until about 600 ml. of distillate was collected. The mixture in the distilling flask was cooled and extracted with ether. The ether solution was washed with saturated sodium bicarbonate, dried over Drierite, and the solvent distilled. The residue was fractionated through a 10-cm. Vigreux column, yielding 36.5 g. (76%) of *t*-butyl β,β-diphenylpropionate, b.p. 159–160° at 1.75 mm. After one recrystallization from methanol the ester melted at 56.5–57.5°; the reported (6) m.p. is 55.5–55.6°.

In a similar manner, methylmagnesium iodide was reacted with *t*-butyl cinnamate and with N,N-diethyl cinnamamide, and ethylmagnesium bromide was reacted with *t*-butyl cinnamate. The products could not be distilled or crystallized. Only small amounts of impure acids could be isolated after refluxing the products with 48% hydrobromic acid. *t*-Butylmagnesium chloride was reacted with methyl cinnamate but, after refluxing the product with 20% sodium hydroxide, the only product isolated was cinnamic acid (3%).

Reactions of amino bases with cinnamic acid derivatives. The reactions with the sodio amines were carried out by adding an ether solution of the cinnamic acid derivative to a liquid ammonia suspension or solution of sodium amide or of the sodio amine prepared from the appropriate amine and an equivalent of sodium amide in liquid ammonia. After stirring for an appropriate time, excess solid ammonium chloride was added, the ammonia was replaced by ether and the resulting mixture was poured into water. When the product was cinnamamide or cinnamanilide most of it precipitated at this point and was filtered off. The ether phase was extracted several times with 2 *N* hydrochloric acid to remove any amine (see below). The ether solution was then washed with saturated sodium bicarbonate, dried over Drierite and the solvent distilled. Petroleum ether was added to the residue to precipitate amide. After filtering, the petroleum ether was evaporated and the residue fractionally distilled. In the reaction of sodium amide with N,N-diethyl cinnamamide there was obtained a large residue which was refluxed with 10% sodium hydroxide for three hours yielding an oil, b.p. 230–248° at 2 mm., and cinnamic acid (6%).

To the combined hydrochloric acid extracts was added a large excess of potassium carbonate and the amino compound, which separated, was extracted with ether. The ether solution was dried over potassium carbonate, the solvent distilled, and the residue crystallized or fractionated.

The reaction with the aminomagnesium bases was carried out by adding an ether solution of the cinnamic acid derivative to the aminomagnesium base prepared from the appropriate amine and an equivalent of standard ethylmagnesium bromide (18). The mixture was stirred and refluxed for the appropriate time, excess aqueous ammonium chloride was added and the product isolated essentially as described for the sodioamino bases.

The results are summarized in Table III.

SUMMARY

A study has been made of the relative extents of 1,2 and 1,4 additions of certain sodio ketones, Grignard reagents, and metallic amino bases to cinnamic acid derivatives, $C_6H_5CH{=}CHCOX$, as X is varied. In general, with a particular basic reagent, the relative extent of 1,2 addition decreases and that of 1,4 addition increases as X is varied in the following order: Cl, OC_6H_5, OCH_3 or OC_2H_5, $OC(CH_3)_3$, $N(C_2H_5)_2$. The tendency for 1,2 addition appears to be greater and that for 1,4 addition less with sodium amide and related basic reagents than with sodio ketones and phenylmagnesium bromide.

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TABLE III

REACTIONS OF CINNAMIC ACID DERIVATIVES WITH AMINO BASES

CINNAMIC ACID DERIVATIVE	MOLES	AMINO BASE	MOLES	TIME	PRODUCT	M.P. (°C.)	YIELD, %
Ethyl cinnamate	0.1	Sodium amide	0.2	30 min.	Cinnamamide	147–148[a]	76
t-Butyl cinnamate	0.05	Sodium amide	0.1	1 hr.	Cinnamamide	149–150[a]	62
t-Butyl cinnamate	0.05	Sodium amide	0.1	5 min.	Cinnamamide	146–147[a]	27
N,N-Diethyl cinnamamide	0.15	Sodium amide	0.15	1 hr.	N,N-Diethyl-β-aminohydrocinnamamide[b]	b.p. 160–163/2 mm.	17[c, d]
t-Butyl cinnamate	0.05	Sodioaniline	0.05	30 min.	Cinnamanilide	150–151[e]	60
t-Butyl cinnamate	0.05	Anilinomagnesium bromide	0.05	2 hrs.	Cinnamanilide	153.5[e]–154.5	36[f]
t-Butyl cinnamate	0.1	Isobutylaminomagnesium bromide	0.1	3 hrs.	N-Isobutyl cinnamamide	110–111[g]	30[h]
t-Butyl cinnamate	0.1	Sodiomethylaniline	0.1	1 hr.	N-Methyl cinnamanilide[i]	b.p. 192/2 mm.[j]	54
t-Butyl cinnamate	0.08	Diethylaminomagnesium bromide	0.08	10 min.	Di-*t*-butyl ester (X)[k]	81–82	21[l]
Methyl cinnamate	0.1	Diethylaminomagnesium bromide	0.1	10 min.	N,N-Diethyl cinnamamide	68–69[m]	24[n, o]

[a] Literature (21): 147°; identified by the mixed melting point method. [b] The picrate melted at 210–211°. *Anal.* Calc'd for $C_{19}H_{22}N_5O_8$: C, 50.78; H, 5.16; N, 15.59. Found: C, 50.76; H, 5.58; N, 15.40. [c] A trace of cinnamamide also distilled and solidified in the condenser. [d] A run using two equivalents of sodium amide to one of N,N-diethyl cinnamamide gave the same result. [e] Literature (21): 150°. [f] *t*-Butyl cinnamate (40%) was recovered. [g] Literature (22): 114°; the mixed melting point with a sample of N-isobutyl cinnamamide (m.p. 111–112°), prepared from cinnamoyl chloride and isobutylamine, was 110.5–111.5°. [h] *t*-Butyl cinnamate (43%) was recovered. [i] *Anal.* Calc'd for $C_{16}H_{15}NO$: N, 5.90; Found: N, 6.14. [j] Literature (8): 231°/15 mm. [k] *Anal.* Calc'd for $C_{30}H_{43}NO_4$: C, 74.80; H, 9.00; N, 2.91. Found: C, 74.66; H, 8.81; N, 3.07. [l] *t*-Butyl cinnamate (33%) was recovered. [m] Literature (16): 66°. [n] *t*-Butyl cinnamate (28%) was recovered. [o] There was also obtained a compound which was presumably N,N-diethyl β-diethylaminohydrocinnamamide, b.p. 162–168°/2 mm., in 11% yield (based on methyl cinnamate). The methiodide melted at 168–169°. *Anal.* Calc'd for $C_{18}H_{31}IN_2O$: N, 6.70; I, 30.34. Found: N, 6.53; I, 29.87.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF MAINE]

THE ACTION OF AQUEOUS CHLORINE ON s-TRITHIANE[1]

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In a previous paper (1) reference was made to certain unknown substances which are formed along with chloromethanesulfonyl chloride when chlorine acts upon a cold aqueous suspension of s-trithiane. This paper describes an attempt to identify these unknown by-products and to discover the manner in which they are formed.

The system in which the aqueous chlorination of s-trithiane takes place is not ideal for the study of reaction mechanisms. Beginning with three phases, water, solid s-trithiane, and gaseous chlorine, it slowly undergoes change until the aqueous layer has become saturated with hydrogen chloride and the solid phase has disappeared, either by going into solution or by becoming dispersed by surface active transformation products. At one stage neither solid nor non-aqueous liquid phases are in evidence. Further chlorination causes the separation of a heavy oil, the distillation of which has led to the observations reported in this paper.

Previous workers (2) have recognized that formaldehyde and sulfur, the latter in the form of sulfur chloride or sulfate ion, are by-products of the formation of chloromethanesulfonyl chloride from s-trithiane by chlorination in the presence of water. The present study confirms the formation of formaldehyde, sulfate ion and sulfur dichloride and in addition establishes that methylene chloride, carbon tetrachloride, and 1,1′-dichlorodimethyl sulfide are also found in small amounts when the oily products from the complete or incomplete aqueous chlorination of s-trithiane are distilled. Careful fractionation has also revealed the presence of an unknown yellow liquid of high refractive index.

The unknown wax-like white solid previously reported (1) has been identified as trichloromethanesulfonyl chloride, Cl_3CSO_2Cl. This compound does not seem to be derived from chloromethanesulfonyl chloride, $ClCH_2SO_2Cl$, for exhaustive chlorination of a pure sample of the latter does not result in the introduction of additional chlorine atoms. The trichloromethanesulfonyl chloride may result from the oxidation of some intermediate such as trichloromethanesulfenyl chloride, Cl_3CSCl. Although this latter compound was never found among the products of distillation, a sample prepared by the method of Helfrich and Reid (3) readily yielded trichloromethanesulfonyl chloride on aqueous chlorination.

The presence of 1,1′-dichlorodimethyl sulfide among the distillation products suggests that a reaction reported elsewhere has occurred (4).

[1] A portion of this communication is taken from theses presented by Verne G. Simpson and Albert K. Sawyer in partial fulfillment of the requirements for the degree of Master of Science. The remainder describes work done by the senior author under a grant from the Coe Research Fund of the University of Maine.

$$(CH_2S)_3 + 2\ SCl_2 = (ClCH_2)_2S + CS_2 + 2\ HCl + 2\ S$$

There is uncertainty, however, as to whether the reaction shown takes place during the low-temperature chlorination or later during the distillation. The conditions under which 1,1′-dichlorodimethyl sulfide was isolated suggest the latter.

It was hoped that in this study the immediate precursor of chloromethanesulfonyl chloride might be found among the distilled products of partial chlorination but no such compound was found. The chlorination of trithiane was carried out in a non-aqueous medium, however, and from the resulting mixture a small yield of chloromethanesulfenyl chloride, $ClCH_2SCl$, was obtained. This substance, when placed in water and further chlorinated, is readily transformed into chloromethanesulfonyl chloride and may well be a short lived intermediate along one path whereby chloromethanesulfonyl chloride is formed. If one accepts this postulate, the great reactivity of the chain hydrogens of aliphatic sulfenyl chlorides (5) offers a possible explanation for the origin of trichloromethanesulfenyl chloride and subsequently the corresponding sulfonyl chloride and carbon tetrachloride (6).

EXPERIMENTAL PART

Chlorination procedure. Finely ground trithiane was suspended in four to five times its weight of water in a three-neck flask fitted with mechanical stirrer. The flask was cooled by a mixture of ice and salt and chlorine was passed in at such a rate that the temperature did not rise above 10°. For complete chlorination the reaction was continued until a permanent color of excess chlorine appeared in the liquid. For partial chlorination the reaction was interrupted at various times, the flask weighed, and any liquid products siphoned off, dried and saved for distillation.

Table I indicates the course of a typical partial chlorination of 100 g. of *s*-trithiane in 400 g. water.

Distillation. In the analytical distillations to identify intermediate products a Todd Precise Fractionation Assembly was employed (7). In a typical run, 150 g. of the combined liquid products from the experiment described above was distilled using an 8 to 1 reflux ratio during the early part of the distillation but a more rapid rate toward the end. Weighed fractions of 1–2 g. were taken and the refractive index of each determined. Weight-refractive index and weight-boiling point graphs revealed the presence of the various components. The relative abundance of the principal fractions is shown in Table II.

Fractions A and B were treated with dilute sodium hydroxide solution to remove traces of sulfur dichloride and were then redistilled. Methylene chloride and carbon tetrachloride were identified by their boiling points and refractive indices.

Fraction C was collected as three portions of 1.0, 0.7, and 0.8 g. having refractive indices of n_D^{20} 1.5362, n_D^{20} 1.5509, and n_D^{20} 1.5368 respectively. The middle portion was analyzed.

Anal. Found: Cl, 64.34; S, 19.71

Atomic ratio: Cl:S = 2.92:1.0

Identification of 1,1′-dichlorodimethyl sulfide. The first 45 g. of liquid products to separate from another partial chlorination of 100 g. of *s*-trithiane was distilled at atmospheric pressure. There was much decomposition but 8 g. of colorless liquid boiling at 155–156° (760 mm.) and 61–62° (26 mm.) was obtained, n_D^{20} 1.5275. This liquid proved to be 1,1′-dichlorodimethyl sulfide, $ClCH_2SCH_2Cl$.

Anal. Calc'd for $C_2H_4Cl_2S$: Cl, 54.12; S, 24.47.

Found: Cl, 53.96; S, 24.42.

Sulfate ion formation during aqueous chlorination. In four trials in which the chlorina-

tion of 40 g. of *s*-trithiane suspended in 200 ml. of water was carried to completion, the aqueous layer was analyzed for sulfate ion. For each mole of *s*-trithiane the respective yields of sulfate ion were 0.699, 0.703, 0.699 and 0.656 mole.

Preparation of chloromethanesulfenyl chloride, $ClCH_2SCl$. One hundred grams of dry *s*-trithiane suspended in 400 g. of anhydrous carbon tetrachloride was treated with chlorine by the same method previously described. The flask was weighed from time to time and the reaction was terminated when three moles of chlorine per mole of *s*-trithiane had been absorbed.

The carbon tetrachloride was removed at atmospheric pressure and the remaining yellowish-red liquid was distilled at reduced pressure. Small fractions were taken and

TABLE I

CHLORINATION OF *s*-TRITHIANE

ELAPSED TIME, HRS.	TEMP. °C	WT. GAINED, G.	OBSERVATION
2	6	86	No apparent change
3¼	4	188	Still much white solid
4¼	5	296	Tan colored solution or emulsion. No heavy liquid settled out
5¾	0	380	43 g. liquid settled out and was removed.
6	0		21 g. liquid was removed
7	1		43 g. liquid was removed
overnight standing			48 g. liquid was removed

TABLE II

FRACTIONATION OF PRODUCTS

FRACTION	B.P./760 MM., °C	WT., G.	CHIEF COMPONENT
A	40–53	3.5	CH_2Cl_2
Intermediate	53–66	1.0	
B	66–75	10.0	CCl_4 and SCl_2
Intermediate	75–117	3.0	
C	117–121	2.5	Unknown yellow compound
Intermediate	121–168	10.2	Probably $ClCH_2SCH_2Cl$ and $ClCH_2SO_2Cl$
D	168–170	90.6	$ClCH_2SO_2Cl$
Residue and loss		26.4	

their refractive indices plotted against total weight of distillate. Five fractions had similar refractive indices but two of these comprising twenty grams were identical and furnished liquid for further study.

The bright yellow liquid was soluble in ether, alcohol, and carbon tetrachloride but insoluble in water and had the following properties: n_D^{20} 1.5434, d_4^{20} 1.5613, b.p. 64° (100 mm.), 30–32° (17 mm.). Molecular weight in benzene; 136, 137. Calc'd for $ClCH_2SCl$; 117.

The measured value for the molecular refraction as determined by the Lorenz-Lorenz equation is 23.63. The calculated value for $ClCH_2SCl$, using the atomic refractions for the Na_D line (8) (employing the mercaptan value for sulfur, 7.69, for want of a better value) is 24.24.

Anal. Calc'd for CH_2Cl_2S: Cl, 60.60; S, 27.40.

Found: Cl, 59.74, 61.18; S, 27.27, 27.87.

A portion of the liquid was chlorinated in cold water and was transformed into chloromethanesulfonyl chloride, the identity of which was established by formation of the *p*-toluidide and comparison with an authentic sample. The aqueous layer from the chlorination tested positive for sulfate ion but negative for formaldehyde.

On standing, chloromethanesulfenyl chloride slowly undergoes decomposition and evolves hydrogen chloride. The index of refraction of one specimen changed over several weeks from n_D^{20} 1.5458 to n_D^{20} 1.559.

Exhaustive chlorination of chloromethanesulfonyl chloride. Forty-four grams of pure chloromethanesulfonyl chloride was placed in 200 ml. of water and chlorinated at 0–1° for 5½ hours. After removal of excess chlorine, 28.5 g. of unchanged starting material was recovered. Distillation through an efficient column showed the complete absence of trichloromethanesulfonyl chloride.

Aqueous chlorination of trichloromethanesulfenyl chloride, Cl_3CSCl. Chlorine was passed into a well-stirred, cold suspension of 5.9 g. of trichloromethanesulfenyl chloride in 100 ml. of water for four hours. The mixture was allowed to warm until the chlorine hydrate had decomposed, air was bubbled through until the color of excess chlorine had disappeared and the solid was separated by filtration. After standing on paper in a calcium chloride desiccator overnight 5.2 g. (75%) of slightly impure trichloromethanesulfonyl chloride was obtained.

Identification and reactions of trichloromethanesulfonyl chloride. s-Trithiane, suspended in cold water was chlorinated to completion. After removal of excess chlorine, washing, and drying, the oil was distilled at reduced pressure through an efficient column. A special still head permitted the collection of the white wax-like solid which first sublimed on a cold finger before turning the slightly higher boiling chloromethanesulfonyl chloride into the downward condenser. The solid always amounted to less than 10% of the final products.

In attempting to identify the unknown solid, hydrolysis experiments were carried out, the exact significance of which was not clear even after the compound was identified as trichloromethanesulfonyl chloride. Small samples were sealed in micro combustion tubes with 5 ml. water and heated at 100° for four hours. On opening the tubes the contents were analyzed for chloride and hydrogen ions, with the following results:

TUBE	WT. SAMPLE, G.	MOLAR RATIO				
		Cl_3CSO_2Cl	:	Cl^-	:	H^+
1	0.1002	1.0	:	2.1	:	4.6
2	0.1331	1.0	:	2.02	:	3.6

The solid melted at 140–141° and was found to have a molecular weight of 214 in benzene solution. Calculated for CCl_4O_2S, 218. The accepted melting point for trichloromethanesulfonyl chloride is 140–140.5°.

Anal. Calc'd for CCl_4O_2S: Cl, 65.09. Found: Cl, 65.37.

No anilide could be formed, and when a sample of the white solid was placed in sodium iodide solution, iodine was liberated. Both of these unexpected reactions are characteristic of trichloromethanesulfonyl chloride (9, 10).

An authentic sample of trichloromethanesulfonyl chloride was prepared and was found to melt unchanged when mixed with the unknown.

SUMMARY

1. The aqueous chlorination of trithiane has been studied and certain previously unrecognized products have been identified.

2. Chloromethanesulfenyl chloride has been prepared and characterized.

ORONO, MAINE

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

THE REACTION OF DIARYLFORMAMIDINES WITH ETHYL MALONATE[1]

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It has been reported previously (1) that the reaction of N,N'-*bis*-(3-chlorophenyl)formamidine with ethyl malonate may be controlled so that the predominant product is the substituted acrylate (II) rather than the anilide (IV) obtained by Dains (2). Compounds of type II are of interest because of the ease with which they may be cyclized to 4-hydroxyquinoline derivatives which are intermediates in the preparation of certain important antimalarial drugs (SN-7618 or Chloroquine, etc.). The present work was undertaken with the purpose of determining the general applicability of the reaction for the preparation of substituted 4-hydroxyquinoline derivatives. Substituted diphenylformamidines are easily obtained in good yield and we have shown that several of these react with ethyl malonate in the same way as the *m*-chloro derivative studied originally. We have encountered an interesting effect of an *ortho*-substituent on the rate of the reaction.

In order to facilitate the investigation of the reaction of ethyl malonate with the formamidines, the acrylates (II) were not isolated, but after removing unchanged formamidine,[3] the crude reaction mixture was subjected to cyclizing conditions, followed by saponification of the quinoline esters (VI) produced; the acids (VII) were precipitated by the addition of mineral acid and their weights taken as a measure of the extent of the first reaction. This is advantageous because it is difficult to separate quantitatively the low-melting acrylates (II) and anilides (IV). Both are cyclized by heating in an inert solvent, but the quinoline anilides (V) are not hydrolyzed by aqueous alkali and separate fairly completely from the alkaline solutions from which they may be removed before acidifying to precipitate the acids (VII). The yield of acrylate from the reaction of a formamidine with ethyl malonate is of course somewhat higher than the value implied by the weight of acid produced, since this figure includes the losses in the cyclization and saponification steps. That these losses are quite low and consistent, however, may be demonstrated by subjecting pure acrylates prepared from ethoxymethylene malonic ester (3) to cyclization followed by saponification under the same conditions employed with the crude acrylates. It is probable that the presence of anilide in the latter lowers the yield in the cyclization step

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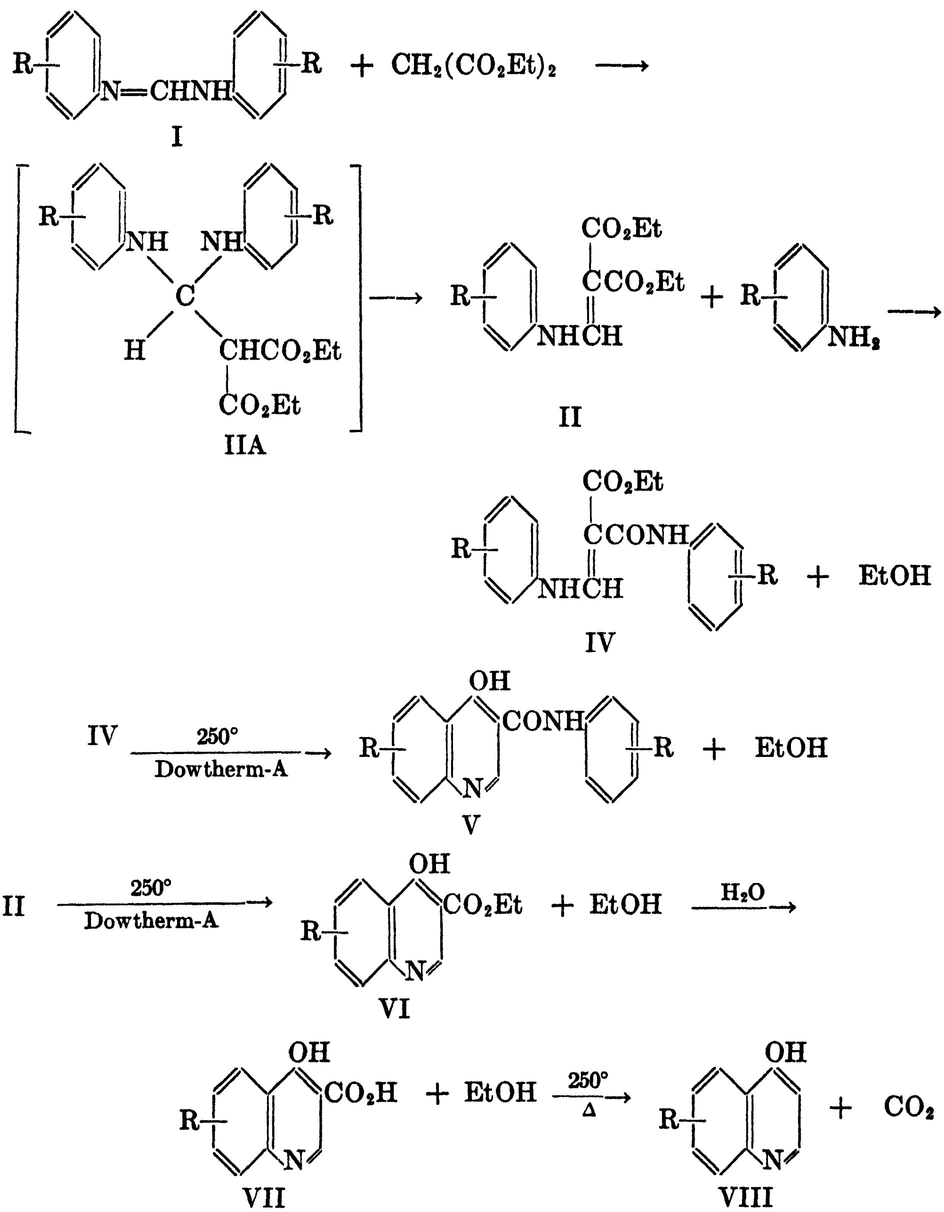
[2] Much of the experimental work was performed by Mr. Marvin B. Edwards and Mr. Russell A. Smith.

[3] The reaction is interrupted at about 40% conversion to (II) in order to prevent excessive aminolyzation of the ester group to produce the anilide (V). The unchanged formamidine may be recovered in good yield by precipitating its insoluble hydrochloride.



somewhat, another factor which makes the yield of the acid represent considerably less than the actual amount of acrylate produced in the first reaction.

The acrylates derived from *o*- and *p*-chloroaniline have been made and cyclized by Tarbell (4), who reported that the *p*-chloro derivative was cyclized under the same conditions as the *m*-chloro and, like it (3), in quantitative yield, but that the *o*-chloro derivative was difficult to cyclize in good yield and gave "by-products." We repeated this work and we found that the *o*- and *p*-chloro derivatives

were cyclized with equal ease under the conditions used previously (3) for the *m*-chloro derivative, giving almost quantitative conversion of the acrylates to 4-hydroxychloroquinoline-3-carboxylic acids. The acrylates derived from ethoxymethylene malonic ester and *o*-, *m*-, and *p*-toluidine were also prepared and converted in good yield to the corresponding 4-hydroxymethylquinoline-3-carboxylic acids.

The treatment of the formamidines with ethyl malonate was carried out at the same temperature for the same length of time as in the original experiment (3) and also at lower temperatures for longer periods in the hope that the rate of the secondary reaction (of the acrylate with aromatic amine) would be retarded more than that of the primary reaction. It was found, however, that the proportion of anilide (IV) to acrylate (II) produced was hardly enough different at the lower

TABLE I

REACTION OF DIARYLFORMAMIDINES WITH ETHYL MALONATE

SUBSTITUENTS ON AROMATIC RINGS	TEMP. (°C)	TIME (HOURS)	PRODUCTS OBTAINED (%)	
			Acid (VII)	Anilide (V)
m-Cl	118	4	36	10
	103	10	39	8
p-Cl	103	10	36	6
o-Cl	103	13	7	
	118	8	18	10
p-CH_3	118	4	31	5
o-CH_3	103	10	15	
	118	8	31	19
m-CH_3	118	4	25[a]	[a]

[a] The yield of acid was probably higher, and an appreciable amount of anilide was produced; but the formation of isomers led to greater solubility and incomplete precipitation of both acid and anilide.

temperatures to offset the inconvenience of a much longer reaction time (Table I); also some of the formamidines do not give homogeneous reaction mixtures at temperatures below 118°.

The yield of 7-chloro-4-hydroxyquinoline-3-carboxylic acid obtained corresponded quite satisfactorily with the results obtained previously when the acrylate was isolated. The behavior of the formamidines prepared from *p*-chloroaniline, *m*- and *p*-toluidine was comparable to that of the *m*-chloroaniline derivative (Table I), but the rate of reaction of the *o*-chloro and *o*-methyl derivatives was much slower. At 118°, twice as long a reaction time was required to give the same per cent yield of acid from the *o*-methyl as from the *p*-methyl derivative, and the rate of reaction of the *o*-chloro derivative was still slower. This is not surprising in view of the fact that the reaction probably proceeds by means of an intermediate addition compound (IIA). [Dains actually pictured such an intermediate in his original paper (2a).] In the formation of this intermediate from the *ortho*-substituted formamidines there would be considerable steric inter-

ference by the substituents on both aromatic rings with the approach of the malonic ester molecule, leading to a decreased rate in the formation of the acrylate (II). It will also be noted that a higher proportion of secondary reaction (producing anilide) occurred with the *o*-substituted formamidines; this is to be expected if the rate of the primary reaction is decreased and that of the secondary reaction remains about the same. The diarylformamidines derived from *o*- and *p*-nitroaniline were prepared but were so insoluble in ethyl malonate at 118° that no appreciable reaction occurred. This reaction seems to offer an interesting opportunity for the study of the effect of substituents on the benzene ring on a type of reaction which has received no attention as far as this aspect is concerned, and we plan to continue such an investigation. It will be more desirable for this work to use an active methylene compound other than ethyl malonate in order to avoid the complication of a secondary reaction.

The separation of the corresponding anilides (V) from the hydroxymethylquinolinecarboxylic acids was less complete than with the chloro derivatives due to the greater solubility of these anilides. Satisfactory separation was obtained in the case of the *o*- and *p*-methyl derivatives by using a smaller volume of aqueous alkali for saponification, but this modification gave no success with the *m*-methyl derivative. Decarboxylation of the crude acid obtained from this compound showed it to contain a mixture of isomers. Ring closure of this acrylate may produce 7-methyl- and 5-methyl-quinoline derivatives, so that a mixture of two anilides and two acids is formed. That this occurred was not surprising, since appreciable isomer formation was noted in the cyclization of the acrylate prepared from ethoxymethylene malonic ester and 3,4-dimethylaniline (6); the surprising thing is the lack of isomer production in the cyclization of the *m*-chloro acrylate. After decarboxylation it was possible to separate the unchanged anilides from the mixture of hydroxymethylquinolines, and the higher-melting 4-hydroxy-7-methylquinoline (5) was isolated easily in pure form. This is the predominant product. The more soluble 4-hydroxy-5-methylquinoline was isolated with difficulty from the mixture in an almost pure state.

The other acids were readily decarboxylated to the chloro- and methyl-hydroxyquinolines which were easily purified and characterized.

EXPERIMENTAL

All melting points are uncorrected. Microanalyses by Clark Microanalytical Laboratory.

Ethyl α-carbethoxy-β-toluidinoacrylates. These were prepared from ethoxymethylene malonic ester and *o*-, *m*-, and *p*-toluidine (3). They were recrystallized from petroleum ether (b.p. 28–38°); all three were obtained in the form of fine white needles. The melting points were: *o*-derivative, 63.5–65°; *m*-, 41–42°; *p*-, 46–47°.

Anal. Calc'd for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91.

Found: (*o*-) C, 64.52; H, 6.74; (*m*-) C, 64.92; H, 6.65; (*p*-) C, 64.83; H, 6.93.

4-Hydroxymethylquinoline-3-carboxylic acids. The acrylates were cyclized in Dowtherm-A (kindly supplied by The Dow Chemical Co.) using a ratio of 200 ml. per 0.1 mole of acrylate. The mixture was heated to reflux for forty-five minutes in an open round-bottomed flask. The quinoline ester was saponified without removing the solvent, which was later separated from the aqueous salt solution with the aid of ether. The aqueous solu-

tion was heated to boiling to remove ether and dilute sulfuric acid was added to the hot solution to precipitate the quinoline acid. After allowing the mixture to cool to room temperature, the acid was collected on a filter and washed with several portions of water. The yield of crude 4-hydroxymethylquinoline-3-carboxylic acids from the *o*- and *m*-toluidino acrylates was practically quantitative (97%) while the *p*-derivative gave 83% conversion. This lower yield was undoubtedly due to the impurity of the *p*-toluidino acrylate used; the analytical sample prepared later had a melting point several degrees higher than that of the sample cyclized. It was found that cyclization of the *m*-toluidino acrylate produced a mixture of 7-methyl- and 5-methyl-4-hydroxyquinoline-3-carboxylic acids. Separation of the isomers was not feasible at this stage so the mixture of acids was submitted for analysis. The acids were best purified by recrystallization from glacial acetic acid, from which they were obtained in the form of fine, colorless needles.

4-Hydroxy-8-methylquinoline-3-carboxylic acid, m.p. 259°, dec.

Anal. Calc'd for $C_{11}H_9NO_3$: C, 65.00; H, 4.47.
Found: C, 65.04; H, 4.42.

4-Hydroxy-6-methylquinoline-3-carboxylic acid, m.p. 257°, dec.

Anal. Found: C, 64.75; H, 4.52.

4-Hydroxy-7(5)-methylquinoline-3-carboxylic acid (mixture), m.p. 246°, dec.

Anal. Found: C, 65.00; H, 4.53.

4-Hydroxy-7-methylquinoline and 4-hydroxy-5-methylquinoline. A 19.8-g. (0.098 mole) sample of the mixed acids (obtained from the cyclization of ethyl α-carbethoxy-β-*m*-toluidinoacrylate followed by saponification) was decarboxylated by heating in 100 ml. of diphenyl ether (kindly supplied by The Dow Chemical Co.) for one hour. The product crystallized slowly from the cool solvent; 100 ml. of petroleum ether (b.p. 28–38°) was added, the mixture was stirred well and filtered. The crude hydroxymethylquinoline was resuspended in petroleum ether and collected again on a filter; it weighed slightly more than the calculated amount (15.5 g.). It was dissolved in 200 ml. of 95% ethanol and the solution was boiled with 2 g. of activated charcoal for fifteen minutes. The charcoal was removed and the alcohol was distilled, leaving 14.1 g. of almost-white solid which was ground in a mortar. The powdered mixture was placed in the cup of a Soxhlet extractor and extracted with 300 ml. of benzene for four hours. Small samples of the undissolved solid were removed every hour, dried, and their melting points determined: after one hour, m.p. 205–215°, sint. 185°; after two hours, m.p. 209–219°, sint. 190°; after three hours, m.p. 214–218°, sint. 205°, after four hours, m.p. 214–218°, sint. 203°. The weight of the undissolved solid when dry was 7.2 g. After recrystallization from water three times there was obtained 5.4 g. of 4-hydroxy-7-methylquinoline, m.p. 223–225°, sint. 190° (5).

There were some crystals present in the benzene when the extraction was stopped. The mixture was allowed to cool and stand overnight and then was filtered; 5.1 g. of crystals were obtained, m p. 155–195°. This material was placed in a Soxhlet cup and extracted further with benzene for a short time. The melting point of the undissolved solid (4.7 g.) was not changed. Crystallization from water was next tried, but the material recovered (4.1 g.) was partially hydrated and still had essentially the same melting range (after drying). An attempt to dehydrate the crystals in boiling toluene was partially successful. A sample treated thus and then recrystallized from toluene melted at 157–160°. The analysis indicated that it still contained a small amount of water.

Anal. Calc'd for $C_{10}H_9NO$: C, 75.40; H, 5.70.
Found: C, 74.65; H, 5.76.
Calc'd for $C_{10}H_9NO \cdot 0.1\ H_2O$: C, 74.64; H, 5.76.

Cyclization of ethyl α-carbethoxy-β-o-chloroanilinoacrylate. Fifteen grams (0.05 mole) of pure acrylate (m.p. 91–92°) was cyclized in 100 ml. of Dowtherm-A (heating forty-five minutes) and the quinoline ester was filtered from the cool solvent and washed with petroleum ether; 12.1 g. (96%) of light tan crystalline 3-carbethoxy-8-chloro-4-hydroxyquinoline was obtained, m.p. 251–255°, sintering slightly from 195°. Recrystallization of the ester from glacial acetic acid, then from a mixture of pyridine and benzene gave 7.2 g. of fine white

leaflets, m.p. 253–255°, sintering from 240°. This was shown to be quite pure 3-carbethoxy-8-chloro-4-hydroxyquinoline by saponification to 8-chloro-4-hydroxyquinoline-3-carboxylic acid, 6.5 g. (100%), and decarboxylation to 8-chloro-4-hydroxyquinoline, 5.05 g. (97%), m.p. 206–212°. Two grams of the last compound were recrystallized from water, 1.5 g. of white needle-clusters being recovered, m.p. 211–213°.

The cyclization was repeated using diphenyl ether as solvent. A 5.1-g. (0.017 mole) sample of acrylate was dissolved in 36 ml. of diphenyl ether and heated to reflux for forty minutes. After the mixture had cooled to room temperature it was filtered and the crystalline product was washed with petroleum ether; when dry it weighed 4.0 g. (93%), m.p. 248–254°, sintering from 195°. One recrystallization from glacial acetic acid gave white leaflets, 3.5 g., m.p. 254–256°, sintering from 195°.

N,N'-bis-(2-chlorophenyl)formamidine. The procedure for the preparation of this compound is described in detail because it is illustrative of the preparation of all the formamidines used in this work and because no satisfactory description of the preparation of formamidines from aromatic amines and ethyl orthoformate was found in the literature.

In a 500-ml. round-bottomed flask was placed 104 g. (0.7 mole) of ethyl orthoformate and 179 g. (1.4 mole) of *o*-chloroaniline. The flask was connected to a 40-cm. Berl saddle-packed column equipped with an electrically heated jacket. The column was kept at 90–100° and the flask was heated in an oil-bath at 145° for about one and one-half hours while ethanol slowly distilled. At the end of this time the oil-bath temperature was raised to 180° and kept there for about one-half hour (or until distillation of ethanol stopped). The reaction mixture was poured out immediately into a porcelain dish because it solidified very quickly on cooling. The crude product (practically quantitative yield) melted at 137–141°; it was recrystallized from dry benzene (a mixture of dry benzene and petroleum ether was used in other runs) giving 150 g. (81%) of colorless prisms, m.p. 139–141°. The analytical sample melted at 141–142°. N,N'-*bis*-(2-chlorophenyl)formamidine has been mentioned in the literature before (6), but no melting point or analytical data are recorded.

Anal. Calc'd for $C_{13}H_{10}Cl_2N_2$: C, 58.90; H, 3.80.
Found: C, 59.25; H, 3.89.

Reaction of N,N'-bis-(3-chlorophenyl)formamidine with ethyl malonate at 118° and at 103°. In a 50-ml. Erlenmeyer flask was placed 13.3 g. (0.05 mole) of N,N'-*bis*-(3-chlorophenyl)-formamidine and 8.0 g. (0.05 mole) of ethyl malonate. The flask was immersed in an oil-bath heated by a thermostatically controlled electric coil (this heating bath was used in all the formamidine and ethyl malonate experiments) to 118° (± 1°) and kept there four hours. The mixture was homogeneous after a few minutes in the oil-bath. After cooling to room temperature, the reaction mixture was dissolved in 85 ml. of benzene and the solution was stirred mechanically while 20 ml. of 10% hydrochloric acid was added dropwise and for fifteen minutes thereafter. The precipitated formamidine hydrochloride was collected, resuspended in 25 ml. of benzene, collected again, and washed with five 15-ml. portions of benzene. All the benzene washings were combined with the first benzene filtrate and washed in a separatory funnel with four 25-ml. portions of water; the benzene solution was next dried over potassium carbonate and the benzene was then removed by distillation. To the residue (containing the acrylate) was added 50 ml. of Dowtherm-A and the mixture was heated to boiling in an open 500-ml. round-bottomed flask for thirty minutes. After cooling the mixture somewhat, 50 ml. of 10% sodium hydroxide was added and the mixture was heated under reflux with mechanical stirring for two hours. After standing for one and one-half hours, the three-phase mixture was filtered and 1.7 g. of solid, m.p. > 300°—undoubtedly 7-chloro-3-*m*-chlorocarbanilido-4-hydroxyquinoline (7)—was collected. The weight corresponded to a yield of 10%. To the filtrate was added 50 ml. of ether and the ether-Dowtherm-A and water layers were separated. The organic solution was washed with 25 ml. of water, this wash was added to the main aqueous solution and this solution was next washed with two 50-ml. portions of ether and then heated to boiling. After cooling slightly, the aqueous solution was made acid to Congo Red paper with 24 ml. of 18% hydrochloric acid. The precipitated 7-chloro-4-hydroxyquinoline-3-carboxylic acid was allowed to stand overnight and was then washed and dried; yield, 4.0 g. or 36%; m.p. 246–247°, dec.

The same amounts of reactants were heated in the oil-bath at 103° for ten hours and the reaction mixture was worked up in exactly the same way. This time 1.4 g. (8%) of the anilide (V) was obtained and 4.2 g. (39%) of the acid (VII) m.p. 254°, dec.

Reaction of N,N'-bis-(4-chlorophenyl)formamidine with ethyl malonate. These reactants (0.05 mole of each) were heated at 103° for ten hours; the formamidine never completely melted or dissolved. After addition of benzene as above, 3.2 g. of unchanged formamidine was recovered by filtration. The remainder of the reaction mixture was treated essentially as described above. One gram (6%) of anilide (V) was obtained and 4.0 g. (35%) of 6-chloro-4-hydroxyquinoline-3-carboxylic acid, m.p. 277°, dec. The acid was decarboxylated in boiling diphenyl ether, the product treated with charcoal and recrystallized from glacial acetic acid, giving 2.7 g. (84%) of 6-chloro-4-hydroxyquinoline, m.p. 262–268°. A second recrystallization gave 2.0 g. of fine white needles, m.p. 268–270° [reported by Tarbell (4) as 261–263°, by Bachmann and Cooper (8) as 269°].

Reaction of N,N'-bis-(2-chlorophenyl)formamidine with ethyl malonate. Equivalent amounts (0.05 mole) of these reactants were heated together at 103° for thirteen hours. As in the above experiment, the formamidine melted and dissolved only partially; this time the mixture was stirred mechanically during the entire heating period. The reaction mixture was worked up as in the preceding experiment. The unchanged formamidine recovered amounted to 7.2 g. The cyclization and saponification steps were also carried out exactly as in the preceding experiment and 0.8 g. (7%) of 8-chloro-4-hydroxyquinoline-3-carboxylic acid was obtained, m.p. 258°, dec. No anilide (V) was isolated.

The same amounts (0.05 mole) of the formamidine and ethyl malonate were heated together at 118° for eight hours; at this temperature the reaction mixture became homogeneous in a few minutes. When worked up in the usual way, no unchanged formamidine was recovered; after cyclization and saponification, 1.9 g. (18%) of 8-chloro-4-hydroxyquinoline-3-carboxylic acid and 1.6 g. (10%) of anilide (V) was obtained. The acid was decarboxylated to produce 8-chloro-4-hydroxyquinoline, m.p. 213–215°, sintering slightly from 205°.

Reaction of N,N'-bis-(4-methylphenyl)formamidine with ethyl malonate. In a small Erlenmeyer flask was placed 22.4 g. (0.10 mole) of the formamidine and 16.0 g. (0.10 mole) of ethyl malonate and the flask was immersed in the oil-bath at 118° for four hours; the mixture was homogeneous almost at once. The reaction mixture was worked up as before with the exception that only one-half the amount of 10% alkali solution used for the chloro derivatives was used in the saponification step. This allowed the separation of the more soluble anilide (V); 1.4 g. (5%), m.p. > 300° was obtained, and 6.3 g. (31%) of 4-hydroxy-6-methylquinoline-3-carboxylic acid, m.p. 257, dec. The acid was decarboxylated to give 4-hydroxy-6-methylquinoline in quantitative yield. One recrystallization from water gave 3 g. of colorless needles, m.p. 234–235°, sintering slightly at 210°. Robson (9) reported the melting point as 227°.

Anal. Calc'd for $C_{10}H_9NO$: C, 75.40; H, 5.70.
Found: C, 75.40; H, 5.71.

Reaction of N,N'-bis-(2-methylphenyl)formamidine with ethyl malonate. A mixture of 10.3 g. (0.046 mole) of the formamidine and 7.4 g. (0.046 mole) of ethyl malonate was heated in the oil-bath at 103° for ten hours. The mixture did not become homogeneous, so it was stirred mechanically during the entire heating period. The reaction mixture was worked up in the usual way; the crude acrylate was cyclized and the quinoline ester saponified to yield 1.4 g. (15%) of 4-hydroxy-8-methylquinoline-3-carboxylic acid, m.p. 259°, dec. This product probably contained some anilide (V) since none was separated.

When the reactants (0.05 mole of each) were heated at 118° the mixture became homogeneous at once. After eight hours, the reaction mixture was worked up as before; there was obtained 2.7 g. (19%) of anilide (V), m.p. 298–305° (not characterized further). The aqueous layer when subsequently acidified yielded 3.1 g. (31%) of 4-hydroxy-8-methylquinoline-3-carboxylic acid, m.p. 258.5°, dec.

The above acid (3.1 g.) was decarboxylated in 15 ml. of diphenyl ether. The crude 4-hydroxy-8-methylquinoline was boiled with 500 ml. of water; the hot mixture was filtered and 0.4 g. of insoluble solid, m.p. 291–> 300°, was collected. [This is evidently partly

anilide (V) but probably represents also some decomposition product of the acid because a water-insoluble substance is always encountered when recrystallizing even the hydroxyquinolines obtained *via* ethoxymethylenemalonic ester, *i.e.*, no possibility of anilide (V).] The aqueous filtrate was treated with charcoal, concentrated, and cooled. There was obtained 1.5 g. of 4-hydroxy-8-methylquinoline, colorless needles, m.p. 212–213°, sintering from 203°. A sample recrystallized for analysis melted at 212–213°, sintering from 206°.

Anal. Calc'd for $C_{10}H_9NO$: C, 75.40; H, 5.70.

Found: C, 75.70; H, 5.68.

Reaction of N,N'-bis-(3-methylphenyl)formamidine with ethyl malonate. One-tenth-mole quantities of the reactants were heated in the oil-bath at 118° for four hours (the mixture became homogeneous immediately). The reaction mixture was worked up exactly as were those from ethyl malonate and N,N'-*bis*-(3-chlorophenyl)formamidine. Only a negligible amount (0.1 g.) of anilide separated from the aqueous solution of the quinoline acid(s) even though the amount of alkali used was that which gave fair separation of the anilide in the case of the *o*- and *p*-toluidine derivatives. This is undoubtedly due to the formation of isomers in the cyclization step, a mixture of two anilides and two acids being produced. The crude mixture of 4-hydroxy-7-methylquinoline-3-carboxylic and 4-hydroxy-5-methylquinoline-3-carboxylic acids precipitated weighed 5.1 g. (25%), m.p. 244°, dec., and evidently contained an appreciable proportion of the mixed anilides, as is demonstrated below.

The crude acid mixture (5.1 g.) was suspended in 25 ml. of diphenyl ether and decarboxylated as before, giving 4.0 g. of crude product. When this material was boiled with 430 ml. of water and the hot mixture was filtered, 0.6 g. of insoluble solid, m.p. > 310°, was collected. Upon cooling, the filtrate deposited droplets of a brown oil, so activated charcoal was added and the mixture was boiled and then filtered. After cooling the filtrate thoroughly in ice, 2.5 g. of white crystals, m.p. 198–216°, sintering from 170°, were obtained. This weight corresponds to 62.5% of the amount of hydroxymethylquinoline calculated from 5.1 g. of acid. Fractional crystallization of this material from water and benzene gave 1.6 g. of 4-hydroxy-7-methylquinoline, m.p. 223–225°, sint. 190°. The isomeric 4-hydroxy-5-methylquinoline was not obtained in a pure state in this experiment.

SUMMARY

The reaction of substituted diphenylformamidines with ethyl malonate to produce acrylates which may be converted readily to 4-hydroxyquinoline derivatives has been shown to be of general applicability. Substituents in the *ortho*- position of the benzene ring were found to have a pronounced effect on the rate of the reaction.

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THE N-ACYLATION OF N-(4-METHOXYPHENYL)-4-CHLOROANTHRANILIC ACID

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In connection with certain studies in the acridine series, the problem arose of N-acetylating N-(4-methoxyphenyl)-4-chloroanthranilic acid (I) without, simultaneously, cyclizing the acid to the corresponding acridone (II). It it generally known that acids of this type show a strong tendency to cyclize under a variety of conditions (1): especially those that would operate in the acetylation of diphenylamine derivatives which, owing to their low order of basicity, require such strongly acidic catalysts as zinc chloride (2), *p*-toluenesulfonic acid (3), sulfuric acid (4), aluminum chloride (4), and perchloric acid (5). Any one of these, in the presence of hot acetic anhydride, would undoubtedly bring about partial, if not complete, cyclization of the above-mentioned acid; an obesrvation which was confirmed experimentally.

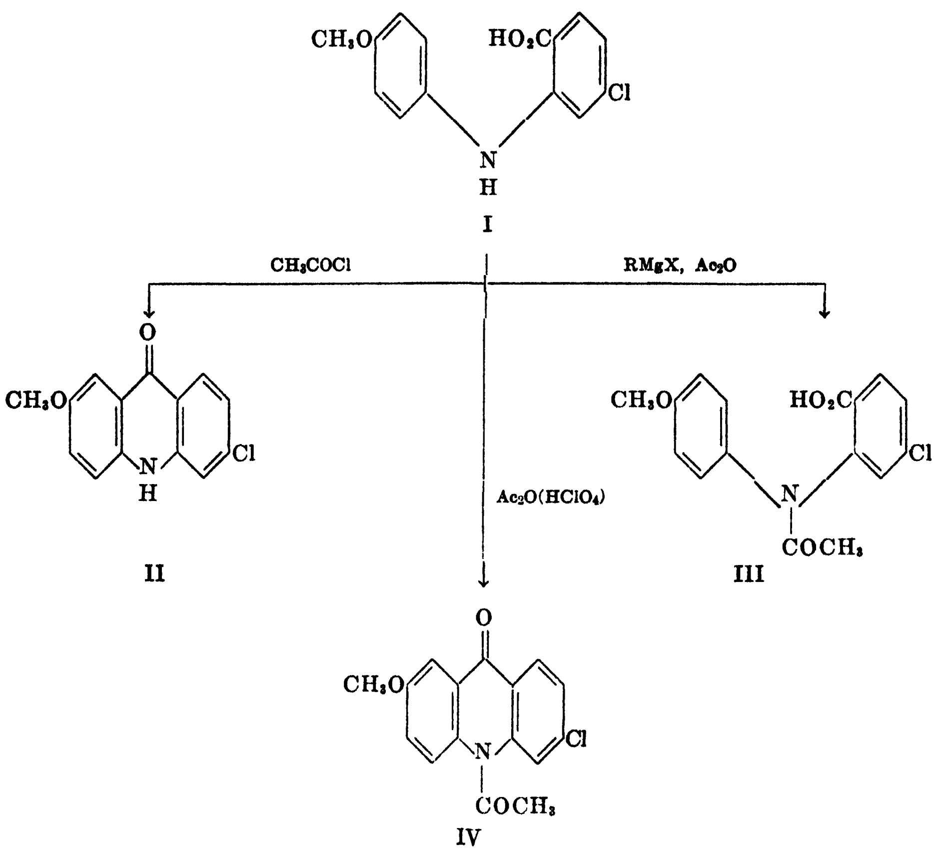
In view of the foregoing, attention was directed to the comparatively mild acetylation technique introduced by Houben (6) for the esterification of certain hydroxyl groups. The method consists of treating the carbinol with a Grignard reagent followed by reaction of the ROMgX compound with acetic anhydride at room temperature. Decomposition of the complex with ice and mineral acid affords the O-acetyl derivative in good yield. A variation of this technique was employed recently by Small and Rapoport (7) in acetylating the tertiary hydroxyl group in 6-methyldihydrocodeine. These investigators substituted methyllithium for Grignard reagent; treatment of the lithium salt with acetic anhydride led to the desired ester. Thus, while this method has proved successful in the acylation of certain, comparatively unreactive, hydroxyl functions it appears, to date, not to have been applied to the imino group.

In the initial application of Houben's technique, the finely powdered diphenylamine carboxylic acid was added to the Grignard reagent. After treating with acetic anhydride, the complex was decomposed with ice and mineral acid and the desired N-acetyl acid (III) obtained in 26% yield. The oily by-products were not investigated. Of the reactive centers present in the original acid, the imino and carboxyl groups would be expected to react first with Grignard's reagent, while the chlorine atom might be regarded as a third (possible) reactive center. It was, therefore, necessary to consider how best to minimize the irreversible coupling reaction which could conceivably occur between the halogen atom and the reagent. When the powdered acid is added *to* the reagent, the latter, present in excess, is potentially capable of reacting with all three reactive centers, either stepwise or concurrently. On the other hand, by reversing the order of addition of reagents, *i.e.*, adding the Grignard reagent to a suspension of the acid in ether, the imino and carboxyl groups, by virtue of their active hydrogens, should instantaneously react with the reagent to the practi-

cally complete exclusion of the chlorine atom. Thus, by-product formation should be diminished and superior yields of the desired product obtained; this has been verified.

The use of methyllithium in this investigation was contraindicated when it was observed that, in addition to reacting with the carboxyl and imino groups, the halogen atom was attacked, *i.e.*, one mole of the acid consumed more than 2 moles of methyllithium (Michler's ketone test).

CHART I



The N-acetyl group is readily hydrolyzed by alkali, under mild conditions, and the original acid results——proof that no structural alterations occurred during acetylation.

Acknowledgment. The microanalyses are by the Analytical Service Laboratory of this Institute.

EXPERIMENTAL

Melting points are uncorrected.

N-Acetyl-N-(4-methoxyphenyl)-4-chloroanthranilic acid. A. Addition of RMgX to the acid. To a stirred and cooled (3°) suspension of 4 g. (0.014 mole) of finely powdered N-(4-

methoxyphenyl)-4-chloroanthranilic acid (8) in 40 ml. of dry ether, 36 ml. (0.035 mole) of approximately 1.0 *M* ethylmagnesium bromide was added during 22 mins. After warming (45°) and stirring for an additional 40 mins. the system was cooled in ice (color change from yellow-orange to light green) and treated with a solution of 3.5 ml. (0.034 mole) of acetic anhydride in 20 ml. of dry ether. The reaction mixture was refluxed for 30 mins. and then mechanically shaken for 12 hrs. Decomposition of the complex was effected with ice and 2 *N* H_2SO_4. The product was taken up in ether, the latter washed with water, dried and concentrated (*vacuo*) to give 2.8 g. (60%) of a yellow, tacky solid. Trituration with cold 3:1 ether-petroleum ether (30–60°) mixture removed most of the oil. Another trituration with a few ml. of cold methanol afforded 2.4 g. (53%) of a virtually colorless, crystalline powder, m.p. 192–194° dec. The N-acetyl derivative crystallizes in small, colorless, truncated prisms from methanol-water; after four crystallizations, m.p. 196–198° dec.

Anal. Calc'd for $C_{16}H_{14}ClNO_4$: C, 60.1; H, 4.41.

Found: C, 60.0; H, 4.43.

The N-acetyl acid is readily soluble either in warm sodium bicarbonate solution or in warm 2 *N* NaOH. On cooling, the sodium salt separates as colorless, hexagonal plates in both cases. Treatment of this salt with cold 2 *N* H_2SO_4 regenerates the N-acetyl acid (m.p. and mixture m.p.).

Deacetylation. A suspension of 0.4 g. of N-acetyl acid in 4 ml. of ethanol was treated with 2 ml. of 40% aq. KOH and warmed on the steam-bath for 2 hrs. Acidification of the cooled solution (2 *N* H_2SO_4) gave 0.3 g. (86%) of a pale yellow solid, m.p. 213–215°; not depressed when mixed with the original N-(4-methoxyphenyl)-4-chloroanthranilic acid.

B. Addition of the acid to the RMgX. In an apparatus similar to that employed above, 5 g. (0.018 mole) of finely powdered N-(4-methoxyphenyl)-4-chloroanthranilic acid was added during 20 mins. to 60 ml. (0.06 mole) of approximately 1.0 *M* ethylmagnesium bromide at 3°. The system was gently warmed (reflux) for 45 mins. then cooled in ice and treated (during 25 mins.) with a solution of 6 ml. (0.06 mole) of acetic anhydride in 40 ml. of dry ether. After refluxing for 30 mins., some lumpy material was broken up and the mixture mechanically shaken for 3 hrs., then kept overnight. The product was worked up as before and gave 1.4 g. (26%) of a nearly colorless solid, m.p. 192–194° dec., identical with the N-acetyl derivative described above.

Direct acetylation attempts. Method I. To a solution of 1.2 g. of N-(4-methoxyphenyl)-4-chloroanthranilic acid in 20 ml. of dry benzene, 3 ml. of acetyl chloride was added and the system refluxed for 2 hrs. Concentration (*vacuo*) and trituration of the residue with 50 ml. of cold, dry ether afforded 1 g. of a yellow solid. A clarified (Norit) solution of this in 8 ml. of methanol was diluted with water (light turbidity) and seeded with the above-described N-acetyl acid. After 15 hrs., 0.5 g. of tan crystals was collected, m.p. 180–190°. A solution of the latter in 4 ml. of methanol was diluted slightly with water; in 3 hrs. 0.2 g. (crop I) of light pink needles separated, m.p. 260–262° dec. The mother liquor, on further dilution with water, deposited yellow needles (crop II). Recrystallized from methanol-water, m.p. 215–216°, alone or in mixture with N-(4-methoxyphenyl)-4-chloroanthranilic acid (starting material).

Recrystallization of crop I from methanol, afforded light-pink needles, m.p. 274–276° dec., insoluble in hot (100°) 2 *N* NaOH. The rather high melting point as well as alkali-insolubility suggest an acridone structure and this appears to be supported by the analytical data required by 2-methoxy-6-chloro-9-acridone.

Anal. Calc'd for $C_{14}H_{10}ClNO_2$: C, 64.8; H, 3.88.

Found: C, 64.9; H, 4.01.

The recorded m.p. for 2-methoxy-6-chloro-9-acridone is given as > 270° (8).

Method II. A suspension of 0.8 g. of the acid in 3.2 ml. of acetic anhydride was treated with one drop of aqueous perchloric acid (60%) and heated on the steam-bath for 8 mins. Addition of ice precipitated an orange oil which solidified to a tacky solid after 24 hrs. Trituration with cold 3:1 ether-petroleum ether (30–60°) mixture removed the oil and left a nearly colorless solid, 0.44 g., m. p. 185–190° dec. A solution of this is 20 ml. of methanol

(Norit) was diluted slightly with water. Overnight, 0.1 g. of small, nacreous plates separated, m.p. 293–295° dec. After two crystallizations, m.p. 301–303° dec. The substance was insoluble in hot 2 *N* NaOH and the analytical data agree with the values required by N-acetyl-2-methoxy-6-chloro-9-acridone (IV) indicating that, to a certain extent, concurrent cyclization and N-acetylation had taken place.

Anal. Calc'd for $C_{16}H_{12}ClNO_3$: C, 63.7; H, 4.01.

Found: C, 63.7; H, 4.21.

The aqueous-methanolic mother liquor was strongly diluted with water; overnight, 0.2 g. of a practically colorless solid separated, m.p. 190–193° dec. The substance was freely soluble in 2 *N* ammonium hydroxide as well as in 2 *N* sodium hydroxide; from the latter the characteristic sodium salt separated in colorless, hexagonal plates. Recrystallization of the acid from methanol-water afforded clusters of colorless prisms, m.p. 192–194° dec. alone or in mixture with the N-acetyl acid obtained by Houben's method.

In repeating the above experiment at 85°, using one drop of 30% perchloric acid as catalyst, the desired N-acetyl acid (m.p. 192–194° dec.) was obtained in ca. 30% yield; the remainder of the product consisted of starting material. Numerous, standard acetylation procedures afforded only unchanged starting material.

SUMMARY

The N-acetylation of N-(4-methoxyphenyl)-4-chloroanthranilic acid by two procedures is described.

The formation of N-acetyl-2-methoxy-6-chloro-9-acridone in one of the acetylation attempts has been observed.

BETHESDA 14, MD.

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[CONTRIBUTION FROM THE PRIVATE LABORATORY OF H. C. WATERMAN, AND FROM THE NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTES OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

DIRECT RING-CLOSURE THROUGH A NITRO GROUP IN CERTAIN AROMATIC COMPOUNDS WITH THE FORMATION OF NITROGEN HETEROCYCLES: A NEW REACTION

HENRY C. WATERMAN AND DONALD L. VIVIAN

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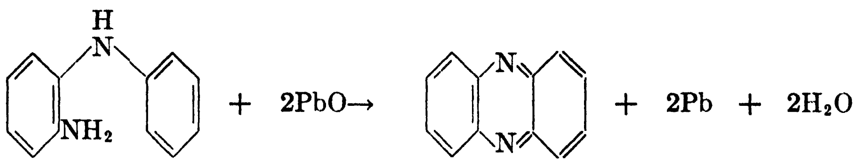
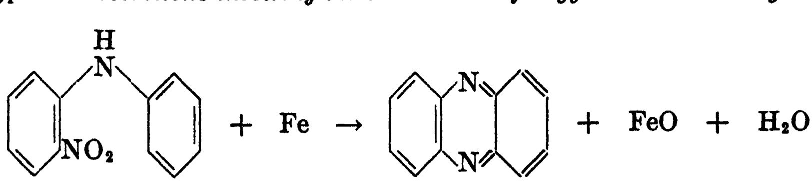
The possibility of synthesizing a nitrogen heterocycle by acting on a nitro compound in such a manner as to effect direct ring closure first suggested itself as a result of our experience with the Fischer and Heiler (1) method for the preparation of phenazine. Their reaction involves oxidation of 2-aminodiphenylamine by dry distillation with litharge:



Our experience with this reaction agreed with the observations of McCombie, Scarborough, and Waters (2), who reported yields "always of the order of 5%." Consideration of the synthesis led to the idea that the whole procedure of reduction of the 2-nitrodiphenylamine to the amino compound followed by oxidation of this to phenazine might be replaced by a new reaction: a reduction of the nitro compound which gave no opportunity for amine formation, but which would take place under conditions favorable to direct ring closure. The choice of a reagent to be employed in attempting to carry out this idea fell upon metallic iron, since we had previously found that Fe_2O_3 could be advantageously substituted for litharge in the Fischer-Heiler synthesis. It seemed not improbable that iron, alone, acting upon the nitro compound at a sufficiently high temperature might produce the same thermostable compound, phenazine, as is produced by the action of iron oxide on the amino compound. This was found actually to occur, and the preliminary results were first made known in the form of a patent (3). The present paper amplifies and extends the reaction, and presents it from the standpoint of five well-differentiated types. The first of these illustrates the general nature of the reaction:[1]

Type A. Reactions involving the elimination of oxygen and water only.



[1] It must be noted that throughout these reactions we have not determined what oxide or oxides are formed; FeO may be the first product, or varying proportions of Fe_2O_3 and Fe_3O_4 may arise; the equations are arbitrarily balanced.

The ease with which the reaction takes place and the stability of the products permit reductants of a considerable range of activity to produce phenazines both from 2-nitrodiphenylamine and from some of its substitution products. A few milligrams of red phosphorus, as an extreme example, reacted so violently with a corresponding quantity of 2-nitrodiphenylamine as to take fire, but phenazine enough for identification sublimed. As an opposite extreme, even an activated decolorizing carbon was found capable of effecting the ring closure with little difficulty. Sulfur likewise yielded phenazine. Granulated lead compared favorably with iron and, in some instances, appeared the better reagent. Some usually quite active metallic reductants, on the other hand, reacted with 2-nitrodiphenylamine very feebly if at all. Among these were aluminum, amalgamated aluminum powder, zinc, magnesium, and calcium.

Iron, lead, and other reductants thus far used in preparing phenazines by nitro group ring closure seem not to react under the given conditions with the water formed in the reaction. The presence of calcium oxide or other dehydrating agent effected no apparent improvement in the yield of phenazine, and heating 2-nitrodiphenylamine with dehydrating agents alone (calcium chloride, calcium oxide, zinc chloride, and phosphorus pentoxide) failed in every instance to give any evidence of the formation of phenazine or phenazine oxide.

Attempts to carry out the reaction in a closed system resulted in a considerable amount of highly-colored material and little or none of the desired phenazine. Hydrogen reduction, due to reaction of iron with the confined steam, appeared the most probable cause of failure under these conditions.

Numerous substituted phenazines can be obtained in varying yield from the correspondingly substituted 2-nitrodiphenylamines without any apparent substantial modification in the reaction, which is designated Type A, to differentiate it from other forms to be described.

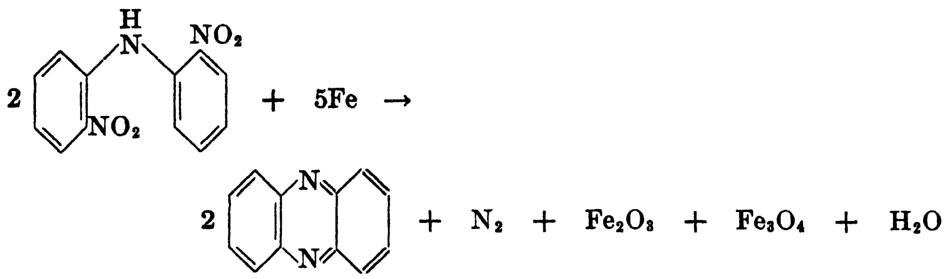
The additional nitro group of 2,4-dinitrodiphenylamine and of 2,4-dinitro-4′-hydroxydiphenylamine rendered the reaction so violent that no product could be isolated. Less violent reactions of both compounds were obtained, however, in preliminary experiments with paraffin as a diluent, and further work is planned to establish the nature of the products.

In general, it seems possible that a large proportion of the ring closures that can be carried out by oxidation of an amino group can be brought about more directly and in many instances in improved yield, by operating on the corresponding nitro compounds with suitable oxygen abstractants in such a manner as to avoid supplying hydrogen to the reaction.

The experimental part of this paper gives details of the synthesis of 2-chlorophenazine and of 2-methoxyphenazine as further examples of the Type A reaction.

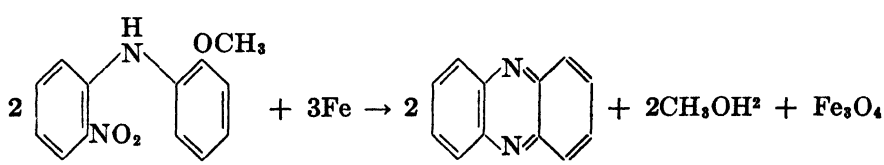
In a recent communication P. Z. Slack and R. Slack (4), have both confirmed and extended our own findings. These authors also rediscovered independently two peculiarities of the reaction which, though observed by us before filing the patent application, could not find place in a statement restricted to the disclosure of potentially industrial processes. These independent observations, both of which go somewhat beyond our own, are more specifically acknowledged below under the topics to which they apply.

Type B. Reactions in which a substituent is eliminated. A reaction of this type was first encountered in the very curious behavior of 2,2′-dinitrodiphenylamine. On heating with a large excess of iron filings in the absence of a diluting solvent, this compound gave a relatively poor yield of unsubstituted phenazine, together with elementary nitrogen.



The volume of the gas evolved corresponded considerably more closely with the elimination of one of the two nitro groups than did the quantity of phenazine isolated. The comparative rarity of an elimination of elementary nitrogen in organic syntheses other than those involving diazonium compounds makes the course of the reaction more obscure. Slack and Slack (4) make the same comment. It is possible, however, that the second nitro group is eliminated as the elements of HNO_2, and that the nitrogen arises from reaction of these with the hot iron.

The loss of a 2′-substituent was again observed in an attempt to prepare 1-methoxyphenazine from 2-methoxy-2′-nitrodiphenylamine. Unsubstituted phenazine was again the only solid product isolated:



This loss was not entirely unforeseen, however, in that McCombie, Scarborough, and Waters (2) had observed the loss of the same substituent from 2-amino-2′-methoxydiphenylamine in the lead oxide procedure. Since the loss of the 2′-methoxyl group was not mentioned in our patent (3), due to its unimportance therefor, Slack and Slack (4) were unaware of our experience with it. They not only made the same observation completely independently, but extended the reaction to show further that alkoxyl groups generally are eliminated in the same way. We do not feel, however, that any "prior reduction" need be postulated, whatever the mechanism of the reaction may be.

Ferrous oxalate (source of active ferrous oxide) as oxygen abstractant for nitro-group ring closures of types C and E. Metallic iron,[3] though often not the most satisfactory reagent, has thus far brought about the ring closures designated as

[2] Formation of CH_3OH assumed; not proved by isolation.
[3] "Activated" iron was not employed.

Types A and B, but has consistently refused to induce ring closures of Types C and E, described below. Iron was not used in our one Type D ring closure (that of unsubstituted benzocinnoline), but Slack and Slack (4), in their independent discovery of the same extension of the basic reaction, used "reduced iron."

A reductant capable of bringing about reactions of Types C, D, and E (as well as of Types A and B) was ultimately found, however, in ferrous oxalate; a reagent which has not, so far as we know, hitherto found use in organic synthesis.

Though very stable at room temperatures, and apparently quite free from the tendency of most ferrous salts to combine with atmospheric oxygen, ferrous oxalate decomposes when heated to a suitable temperature (widely misstated as between 150° and 160°) to yield carbon monoxide and dioxide and a pyrophoric form of ferrous oxide; the last-named compound being, of course, the actual oxygen-abstracting agent sensitive enough to induce the reactions which iron, lead, etc., had failed to bring about. Since the nitro compound can be thoroughly mixed with the oxalate, either dry or in a suitable solvent of sufficiently high boiling point, the tendency of the ferrous oxide to ignite on exposure to air causes no difficulty; the pyrophoric material is in contact, at the moment of its formation, with the nitro compound upon which it is to act. Also, the carbon monoxide and dioxide from the oxalate undoubtedly have some protective effect.

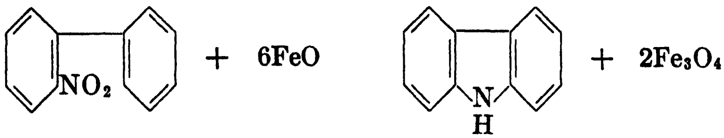
The temperature range 150° to 160°, often given as that within which ferrous oxalate yields oxides of carbon and ferrous oxide, is actually the range observed by J. von Liebig (5) as that of a partial dehydration of the dihydrate, $FeC_2O_4 \cdot 2H_2O$, to a sesquihydrate, $(FeC_2O_4)_2 \cdot 3H_2O$. A paper (6) of the same early date indicates a considerably higher temperature (about 194°) is required to break up the oxalate radical, and also states that the pure salt cannot be obtained anhydrous.

We have found that anhydrous FeC_2O_4 can be prepared, however, if oxidation is prevented by suspending the hydrated salt in mineral oil and the heating carried out under proper conditions. The anhydrous oxalate is preferable when the evolution of the water content of the dihydrate is a disadvantage. Anhydrous ferrous oxalate has, in some instances, lost its activity when held for long periods. Whether the anhydrous oxalate will remain active indefinitely when kept under oil has not yet been determined.

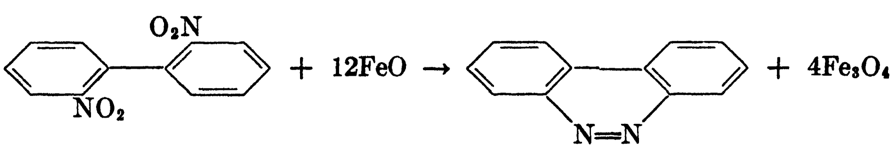
A wide divergence in activity among commercial preparations of ferrous oxalate has been encountered. Some lots have appeared to be at least partially dehydrated, and some have been found to contain varying quantities of contaminants. None of the commercially available ferrous oxalate, though obtained from a number of standard sources, has been found to be labeled definitely as $FeC_2O_4 \cdot 2H_2O$. In view of these variations in the commercial product, the exceedingly simple preparation of the reagent from ferrous sulfate and oxalic acid should probably be carried out in the laboratory. Alkali-metal or ammonium oxalates form complexes with ferrous oxalate which are both difficult to wash out of the precipitate and are, in addition, very easily oxidized by atmospheric oxygen. Neither these nor ferrous ammonium sulfate should be used in the preparation of the ferrous oxalate reagent. Precipitation from ferrous sulfate with oxalic acid

has thus far yielded a dependable form of the reagent. The presence of small quantities of the complex salts above mentioned seems a very probable cause of some of the variations in behavior of the commercial product.[4]

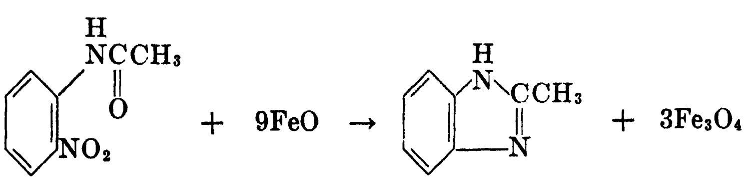
The type C reaction. This form of nitro group ring closure, the first in which no hydrogen is eliminated from the nitro compound, is exemplified in the formation of carbazole from 2-nitrobiphenyl.

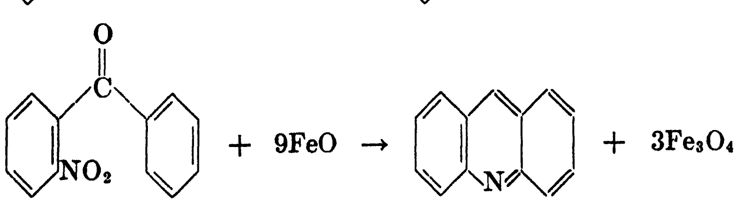


The type D reaction. Unique among the nitro group ring closures thus far effected, in that the ring is closed between nitrogen and nitrogen rather than between nitrogen and carbon, this type of reaction has been encountered by us only in the formation of 3,4-benzocinnoline (with no trace of the compound sought) in an attempt to obtain 4-nitrocarbazole from 2,2′-dinitrobiphenyl. Though of much scientific interest, this observation was regarded as negative from the viewpoint of our patent (3) and was not mentioned therein. The finding of Slack and Slack (4) that our reaction "also provides a new process for the synthesis of benzocinnolines" represents, therefore, a quite independent discovery by them of the benzocinnoline ring closure; too, they found that "reduced iron" will effect the reaction, carried out by us with ferrous oxalate. This latter may be formulated:



Reactions of type E. These reactions, which involve the removal of a carbonyl oxygen atom as well as the oxygen atoms of the nitro group, are illustrated in the synthesis of 2-methylbenzimidazole and of acridine.





[4] Since the oxalate is too costly a source of ferrous oxide for most industrial uses, reduction of higher oxides by gases (producer gas or water gas) has been given some attention.

The reactions selected as experimental illustrations of those aspects of the nitro group ring closure dealt with in this paper are not violent when carried out with the quantities and in the proportions specified. The large excess of the reductant which has always been used when iron or lead was the reagent of choice effects a considerable dilution; and in the use of ferrous oxalate, relatively great dilution is inherent in the molecular weight and bulk of the reagent itself.[5] Caution may be advisable, however, in the use of smaller excesses of the reductants (especially if these be very finely divided, or pretreated to activate them), or in the use of nitro compounds the properties of which, with respect to the nitro group ring closure, are not known. The extremely vigorous reaction of 2,4-dinitrodiphenylamine and of its 4′-hydroxy derivative have already been noted with the Type A reactions. The *dry* reaction of both these 2,4-dinitro compounds with ferrous oxalate, though only about 0.2 g. of either nitro compound was used, was still more violent, ejecting the pyrophoric FeO from the test tube as a small shower of sparks.

EXPERIMENTAL

Phenazine.[6] One hundred grams of 2-nitrodiphenylamine was thoroughly mixed with 1 kg. of 20-mesh degreased iron filings in a 1-liter long-neck round-bottomed flask. The mixture was then heated in an oil-bath, which was brought up to a maximum temperature of 300°. Heating was continued for approximately 30 minutes after the bath had reached 280°; this was about 10 minutes longer than the time required for the disappearance of all red color in the material on the side walls.

Complete extraction of the reaction mixture with ether gave 61 g. of dark brown solid, which on vacuum distillation followed by recrystallization from benzene (Norit) gave 38.5 g. (46%) of light yellow product melting at 174.7–176.3°, (cor).

Anal. Calc'd for $C_{12}H_8N_2$: N, 15.6. Found: N, 15.5.

Phenazine from 2-methoxy-2′-nitrodiphenylamine. Five grams of 2-methoxy-2′-nitrodiphenylamine was mixed with 50 g. of 20-mesh degreased iron filings in a round-bottomed flask, and the whole heated 30 minutes in an oil-bath at 280–290°. Extraction with ether followed by recrystallization from benzene of the residue left from evaporation of the ether gave 0.7 g. of unsubstituted phenazine, not depressing the melting-point of phenazine made from 2-nitrodiphenylamine. No evidence of any 1-methoxyphenazine was found.

Phenazine from 2,2′-dinitrodiphenylamine. One gram of 2,2′-dinitrodiphenylamine was heated 20 minutes with 10 g. of 20-mesh degreased iron filings in an oil-bath maintained at 280–290°. The reaction was more vigorous than that with 2-nitrodiphenylamine, and a gas

A ferrous oxide giving a yield of carbazole from 2-nitrobiphenyl essentially the same as that obtained in the laboratory by the use of ferrous oxalate has been produced by gas reduction of higher oxides.

Whether the oxygen-abstracting capacity of ferrous oxide is represented by $6FeO + O_2 \rightarrow 2Fe_3O_4$ or by $4FeO + O_2 \rightarrow 2Fe_2O_3$ has not been determined, since it has not been necessary to avoid an excess.

[5] About 540 g. of the dihydrate, or 432 g. of the anhydrous FeC_2O_4, is required, for example, to provide FeO to combine as Fe_3O_4 with the one gram-atom of oxygen removed by the reductant from 1 mole (about 214 g.) of 2-nitrodiphenylamine.

[6] Whether improved yields are possible with this preparation or others through the use of more finely divided iron, or of iron or other metals pretreated in any way, as by reduction, remains to be determined, as does the effect of holding the temperature down to the lowest range in which reaction is initiated.

was evolved. This gas was collected over water and subjected to tests to determine its nature: red phosphorus placed on an electrically warmed copper plate in the gas did not react with it; a bright copper coil electrically heated to a dull red glow for 10 minutes within the gas showed no change, none of a measured volume of oxygen was taken up by it, nor did the gas react with $Ba(OH)_2$ solution. Hence it could only be nitrogen. The amount evolved, corrected for pressure and temperature, corresponded to 83.6% of that calculated for elimination of the nitrogen of one nitro group per mole of the 2,2′-dinitrodiphenylamine. Isolation of the organic product by extraction of the reaction mixture, vacuum sublimation of the extract, and recrystallization from benzene gave 0.1 g. of phenazine, identified by mixed melting point. As in the preceding reaction of 2-methoxy-2′-nitrodiphenylamine, there was no evidence of the formation of any measurable quantity of a substituted phenazine.

2-Chlorophenazine. The preparation of this compound by reacting 4-chloro-2′-nitrodiphenylamine with iron filings gave comparatively poor results; those with 4-chloro-2-nitrodiphenylamine were distinctly better.

As with the unsubstituted intermediate, 100 g. of 4-chloro-2-nitrodiphenylamine was heated in a 1-liter flask with 1 kg. of 20-mesh degreased iron filings by an oil-bath held at 280–295° for about 40 minutes. The reaction is somewhat more vigorous than that with 2-nitrodiphenylamine; the internal temperature reaches a maximum of 348° and there is a copious evolution of fumes. Ether extraction of the reaction mixture followed by sublimation at 1 mm. from an oil-bath at 115° gave 30.0 g. of sulfur-yellow 2-chlorophenazine mixed with a small amount of darker orange material; this combined product melted at 136–139° after softening at 133°. Recrystallization from methanol gave 25.8 g., (30%), melting at 137.7–138.9°, cor. McCombie, Scarborough, and Waters (2) give 139° as the m.p. of 2-chlorophenazine.

Anal. Calc'd for $C_{12}H_7ClN_2$: C, 67.2; H, 3.27; Cl, 16.5; N, 13.1.
Found: C, 67.5; H, 3.29; Cl, 16.9; N, 12.9.

2-Methoxyphenazine.[7] Eight grams of 4′-methoxy-2-nitrodiphenylamine was mixed with 20 g. of anhydrous ferrous oxalate and 80 g. of granulated lead, and the whole heated for 30 minutes in a bath at 265–282°. The reaction is vigorous, with the evolved water issuing as steam. Vacuum distillation applied to the entire reaction mixture gave 3.45 g. (49%) of yellow material melting at 119°. This on recrystallization from water, or better, chromatographic adsorption on alumina, gave pale yellow crystals melting at 123.1–123.7°, cor. McCombie, Scarborough, and Waters (2) give 126° as the m.p. of 2-methoxyphenazine.

Anal. Calc'd for $C_{13}H_{10}N_2O$: C, 74.3; H, 4.8; N, 13.3; CH_3O, 14.8.
Found: C, 74.3; H, 4.7; N, 13.0; CH_3O, 14.7.

Carbazole. One gram of 2-nitrobiphenyl was thoroughly mixed with 12 g. of ferrous oxalate dihydrate, and the mixture heated in an oil-bath for 30 minutes at an internal temperature of 205–215°. Water was given off from the oxalate during the heating, an inconvenience causing loss of material which can be obviated by the use of anhydrous oxalate.

A total of 0.45 g. of carbazole sublimed from the reaction mixture; boiling the reaction residue with toluene, and recrystallizing the extracted material from the same solvent yielded a further 0.075 g. (Total yield 63%). The product was identified by its m.p., 240°, not depressed by mixture with an authentic specimen of carbazole, as well as by the usual color reactions, odor, and crystalline form.

3,4-Benzocinnoline. Five grams of 2,2′-dinitrobiphenyl was thoroughly mixed with 50 g. ferrous oxalate dihydrate[8] and heated in an oil-bath to an internal temperature of 200°,

[7] We found that admixture of granulated lead with the reaction mixture gave better results than did the oxalate alone, in part due to better heat conduction through the mixture.

[8] This is the only instance observed by us, so far, in which the anhydrous oxalate appears to give less satisfactory results than does the dihydrate. The preponderance of the dihydrate in our reported procedures is due to the fact that most of these were made before we discovered the possibility of using the anhydrous form.

which was gradually increased to a maximum of 245° over a period of about 50 minutes. Evolved water was conducted off by a side arm. The flask was stoppered and allowed to cool to room temperature; the contents could then be poured out in the air without igniting. The precaution of allowing the mixture to cool must be taken before subjecting it to ether extraction, since the pyrophoric FeO can produce vigorous sparking. Thorough extraction with ether produced 1.7 g. (46%) of yellow-brown crude product, melting at 130–148°. This on two recrystallizations from 50% alcohol (Norit) gave 0.64 g. (17%) of yellow crystals with a slight greenish tinge, melting at 154.7–156.3°, (cor.). Täuber (7) gives 156° as the m.p. of 3,4-benzocinnoline.

Anal. Calc'd for $C_{12}H_8N_2$: N, 15.6. Found: N, 15.8.

2-Methylbenzimidazole. A mixture of 1.8 g. of 2-nitroacetanilide and 18 g. of ferrous oxalate dihydrate was heated to an internal temperature of from 220° to 225° and kept at that temperature for about 30 minutes. The cooled reaction mixture was extracted with hot alcohol, yielding yellow-brown amorphous material containing a lighter-colored crystalline substance. Boiled with several small portions of water, this gave traces of brown insoluble matter and a yellow solution, paler after treatment with Darco. Concentrated to crystallization, the solution yielded rosettes of stubby, very slightly yellowish needles, m.p. 173.5°, unchanged by mixture with authentic 2-methylbenzimidazole; yield, 0.51 g. (42%).

Acridine. The few milligrams of 2-nitrobenzophenone which were available reacted with the usual excess of ferrous oxalate dihydrate (about 20%) to yield a small quantity of a sublimate of flaky white crystals of which the melting point was 105–106°. These gave a strong bluish fluorescence in alcoholic solution, and fluoresced quite strongly in the solid state when subjected to a high-frequency glow discharge under 1 mm. pressure, emitting light of a pale blue color. Their vapors were highly irritating to eyes and nostrils. Although loss of the product prevented taking a mixed m.p., the agreement of the properties described with those of acridine, and the method of synthesis would seem to establish a strong probability for identity of the product with acridine.

Anhydrous ferrous oxalate. A charge of 432 g. of ferrous oxalate was placed in a three-neck flask fitted with a mechanical stirrer, thermometer, and descending condenser. Light mineral oil was added until there was a layer about 1 cm. deep above the surface of the oxalate. The stirrer was started, and the flask heated in an oil-bath. (If stirring is not adequate, or if the heating is uneven, partial decomposition of the oxalate occurs.)

Water was not evolved until an internal temperature of about 176° was reached (oil-bath at 200°); at this point evolution of steam set in. The internal temperature was gradually raised to a maximum of 195° over a period of 80 minutes. The evolution of steam, which had increased at first, fell off during the last 30 minutes, and had practically ceased by the end of the 80 minutes. A total of 75 cc. of water was collected, as against the theory of 86.4 g. based on the formula $FeC_2O_4 \cdot 2H_2O$, but there was a very considerable holdup on the sides of the 5-l. flask used. The flask was opened to the air while still hot, to permit the escape of this water.

The larger part of the dehydrated material was allowed to remain under the surface of the oil, with the object of taking samples for use as need arose, and thus determining whether activity is lost with the passage of time. A sample for analysis was secured by filtering it off from the oil, washing it thoroughly with chloroform followed by benzene, and drying it in a vacuum at room temperature out of light.

Anal. Calc'd for FeC_2O_4: C, 16.7; Found: C, 16.6.

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SUMMARY

A ring closing reaction of certain aromatic nitro groups, brought about by abstracting the nitro group oxygen atoms under conditions preventing their replacement by hydrogen and resulting in heterocycles of which the nitro group nitrogen atom is a member, is shown to occur in several variations, illustrated by closures of the phenazine, carbazole, benzocinnoline, benzimidazole, and other rings.

For nitro group ring closures effected poorly or not at all by iron or lead, use of ferrous oxalate (a source of pyrophoric ferrous oxide at moderately high temperatures) is introduced. It has been possible to obtain this oxalate in an anhydrous state, and use of this new reagent has been found to be advantageous in some instances.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF ROCHESTER]

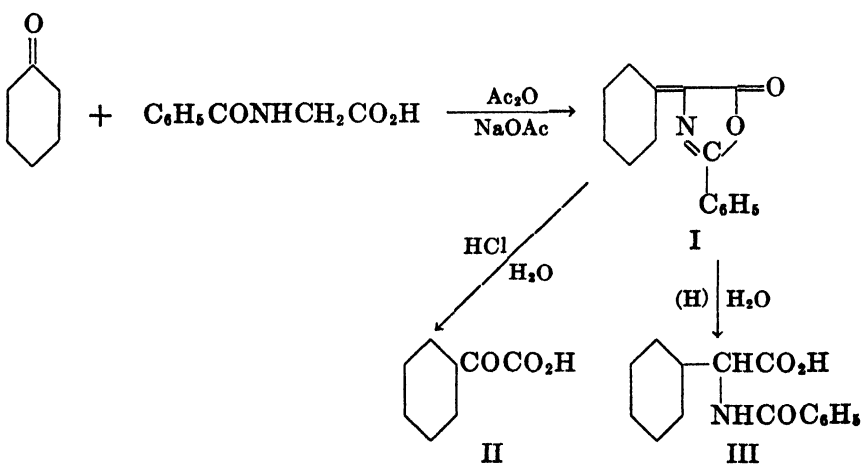
THE USE OF KETONES IN THE ERLENMEYER AZLACTONE SYNTHESIS

V. BOEKELHEIDE AND LOIS M. SCHRAMM[1]

Received October 20, 1948

In certain investigations in this laboratory, it became highly desirable to have a method which would be generally applicable for the conversion of ketones to α-amino acids of the type $R_1R_2CHCH(NH_2)CO_2H$. Although such excellent methods as the Erlenmeyer azlactone synthesis (1), the hydantoin synthesis (2), and the rhodanine synthesis (3) have been worked out for the conversion of aldehydes to the analogous α-amino acids, there are only a few cases in which ketones have been employed in these syntheses. Acenaphthenequinone (4), isatin (5), and alloxan (6) have been reported to undergo condensation with rhodanine. Also, Ramage and Simonsen (7) have reported that the condensation of acetone with hippuric acid gives a fair yield of 2-phenyl-4-isopropylidene-5-oxazolone. In the present investigation the use of ketones in the Erlenmeyer azlactone synthesis has been studied to determine the scope and applicability of the reaction.

When cyclohexanone was treated with hippuric acid under the usual conditions of the Erlenmeyer azlactone synthesis, there was obtained in 49% yield the desired 2-phenyl-4-cyclohexylidene-5-oxazolone, I. The structure assigned to I was substantiated by hydrolysis and reduction experiments. Mild alkaline hydrolysis of I gave an excellent yield of a compound having the properties to be expected for α-cyclohexylidenehippuric acid. On the other hand, hydrolysis with concentrated hydrochloric acid gave a good yield of cyclohexyloxoacetic acid, II. Although the attempted reduction of I with platinum oxide as catalyst was unsuccessful, reduction accompanied by hydrolysis occurred, when Raney nickel was employed as catalyst, and a good yield of α-cyclohexylhippuric acid, III, was obtained.



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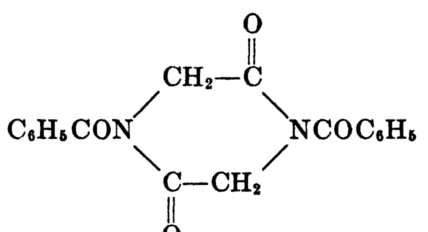
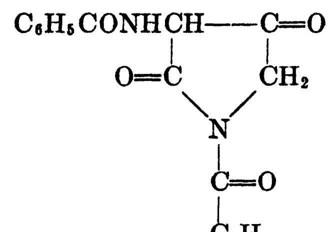
Although the formation of the azlactone of cyclohexanone occurred readily in the expected manner, the reaction took a different course with less active ketones. When the reaction was attempted using methyl ethyl ketone, mesityl oxide, acetophenone, or 2-methylcyclohexanone, there was obtained from each of the reaction mixtures a small yield of a white solid, which melted at 138°. The product was the same regardless of the ketone employed, since no depression of melting point was found for mixtures of samples from different runs. Combustion analysis of the product melting at 138° indicated an empirical formula of $(C_9H_7NO_2)_x$. Furthermore, the product gave a distinct purple ferric chloride test. These properties are in agreement with those which have been reported for a dimolecular product of hippuric acid. This dimolecular product has been obtained by Rugheimer (8) by the action of sodium ethoxide on sodium hippurate; by Curtius (9) from the reaction of hippurazide with alkali; by Scheiber and Reckleben (10) from the reaction of sodiomalonic ester and hippuryl chloride; and by Karrer, Wehrli, Biedermann, and dalla Vedova (11) from the reaction of hippuryl chloride, pyridine, and copper powder. The identity of our product with that obtained by Karrer and his co-workers was established by repeating their preparation and making a comparison of the two samples.

Although Karrer *et al.* assign structure IV to their product, this is probably not correct. Cornforth and Huang[2] (12) have obtained evidence indicating that the correct structure is V. In view of this recent evidence no further investigation of our product was made, and it was assumed to be V.



IV



V

Since the reaction had not taken the desired course with ketones less active than cyclohexanone, the reaction was attempted with a more active ketone, cyclopentanone. However the only product to be isolated in this case, also, was V.

Several attempts were made to obtain the desired condensation of methyl ethyl ketone with hippuric acid by varying the reaction conditions and the length of time of reaction, but these attempts were without success.

EXPERIMENTAL[3]

2-Phenyl-4-cyclohexylidene-5-oxazolone, I. A mixture of finely divided, anhydrous sodium acetate (9.0 g., 0.1 mole), hippuric acid (18.0 g., 0.1 mole), cyclohexanone (30 g., 0.3 mole), and acetic anhydride (35 ml.) was heated with intermittent shaking until the mixture

[2] We should like to thank Dr. H. T. Huang for his kindness in allowing us to examine his doctoral dissertation.

[3] Analyses by Mrs. G. L. Sauvage and the Micro-Tech Laboratories.

had gone from a pink, semi-solid mass to a deep orange liquid (ten to fifteen minutes). The mixture was then cooled to room temperature and the crystalline product, which separated, was removed by filtration. The crude product was recrystallized from ethanol, and there was obtained 11.3 g. (49%) of fine, white needles, m.p. 137–138°.

Anal. Calc'd for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27.

Found: C, 74.56; H, 6.13.

α-Cyclohexylidenehippuric acid. A mixture of 1.0 g. of 2-phenyl-4-cyclohexylidene-5-oxazolone, 0.5 g. of potassium hydroxide, and 15 ml. of water was heated on the steam-bath until solution was complete. On acidification a white solid separated. After recrystallization from ethanol, there was obtained 0.9 g. (85%) of white needles, m.p. 244–246°.

Anal. Calc'd for $C_{15}H_{17}NO_3$: C, 69.47; H, 6.62.

Found: C, 69.35; H, 6.46.

Cyclohexyloxoacetic acid, II. A mixture of 8.0 g. of 2-phenyl-4-cyclohexylidene-5-oxazolone and 50 ml. of concentrated hydrochloric acid was heated on the steam-bath for twenty hours. The precipitated benzoic acid was separated by filtration, the filtrate was extracted with ether, and the ethereal solution was washed with a small amount of water and dried over sodium sulfate. After the ether had been removed, the residual oil was distilled yielding 3.1 g. (60%) of a colorless oil; b.p. 73–74° at 3.5 mm.

Anal. Calc'd for $C_8H_{12}O_3$: C, 61.52; H, 7.75.

Found: C, 61.65; H, 8.10.

α-Cyclohexylhippuric acid, III. A mixture of 8.0 g. of 2-phenyl-4-cyclohexylidene-5-oxazolone, 1 g. of Raney nickel catalyst, and 20 ml. of alcohol was shaken at 100° under a pressure of about 80 atm. of hydrogen. The theoretical amount of hydrogen was absorbed in about forty-five minutes. After separation of the catalyst and removal of the solvent, the crude product was warmed with a 5% potassium hydroxide solution. The material insoluble in potassium hydroxide was removed by filtration, and the filtrate was acidified. The crude acid was collected and recrystallized from alcohol. There was obtained 4.1 g. (55%) of white crystals, m.p. 197–199°.

Anal. Calc'd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33.

Found: C, 68.96; H, 7.21.

The material, which was not soluble in potassium hydroxide solution, was recrystallized from methanol and obtained as white crystals, m.p. 179–180°. This material was not hydrolyzed by boiling with acid or base, and it was not further identified.

When the reduction of 2-phenyl-4-cyclohexylidene-5-oxazolone was attempted using acetic acid as solvent and platinum oxide as catalyst with a hydrogen pressure of 3 atm., no hydrogen uptake was observed and the starting material was recovered. In another attempt, the condensation of cyclohexanone and hippuric acid was carried out with acetic anhydride as solvent, platinum oxide as catalyst, and under a hydrogen atmosphere. It was hoped that condensation would be accompanied by reduction and in this way the reaction would go to completion. However, at temperatures of 80–100° condensation occurred to give I in the usual yield, but no reduced product was isolated.

Attempted condensations of hippuric acid with methyl ethyl ketone, mesityl oxide, acetophenone, 2-methylcyclohexanone, and cyclopentanone. For each of the aforementioned ketones the following procedure was employed. A mixture of anhydrous sodium acetate (9.0 g., 0.1 mole), hippuric acid (18.0 g., 0.1 mole), acetic anhydride (35 g., 0.3 mole), and freshly distilled ketone (0.3 mole) was heated with shaking until the mass became liquid (usually fifteen minutes). The mixture was then heated a few minutes longer, cooled, and poured into water. The insoluble, oily layer was removed and washed by decantation with water. After the oil had been heated *in vacuo* to remove volatile impurities, it set to a thick, red mass. The crude product was treated with charcoal in methanol several times and then recrystallized a number of times from methanol. In this way there was eventually obtained 3.0 g. (18%) of white crystals. The same product in approximately the same yield was obtained regardless of the ketone employed and mixtures of samples from different reaction mixtures showed no depression of melting point.

Anal. Calc'd for $(C_9H_7NO_2)_x$: C, 67.07; H, 4.38.
Found: C, 67.22, 66.88; H, 4.30, 4.27.

The condensation of methyl ethyl ketone with hippuric acid was also tried under conditions in which the reaction mixture was boiled under reflux for several hours, under conditions in which the reaction mixture was heated until it became liquid and was then allowed to stand 24 hours at room temperature, and under conditions in which the ratio of reactants was varied. The only product to be isolated in each case was the material melting at 138° and none of these measures improved the yield of this product.

Peculiarly enough, when the above reaction was carried out without ketone present, no dimolecular product was obtained but instead benzoic acid was isolated. The benzoic acid was probably derived from a transacetylation of the hippuric acid by acetic anhydride.

Identification of the material melting at 138°. The material melting at 138° gave a distinct purple ferric chloride test. This behavior in conjunction with the melting point and empirical formula corresponded to the product which Karrer *et al.* (11) had reported from the reaction of hippuryl chloride, pyridine, and copper powder. The preparation of their product was repeated, and it was found that a mixture of the two samples melted at 138°. As indicated by Cornforth and Huang (12), the material melting at 138° is probably N-benzoyl-2,4-diketo-3-benzamidopyrrolidine, V.

SUMMARY

Cyclohexanone has been found to condense with hippuric acid in the Erlenmeyer azlactone synthesis to give 2-phenyl-4-cyclohexylidene-5-oxazolone. However, with a number of other simple ketones the Erlenmeyer azlactone synthesis with hippuric acid did not give any condensation product but instead gave a dimolecular product which is probably N-benzoyl-2,4-diketo-3-benzamidopyrrolidine.

ROCHESTER, NEW YORK

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[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

CONDENSATION OF AROMATIC ALDEHYDES WITH γ-PICOLINE METHIODIDE

ARTHUR P. PHILLIPS

Received October 27, 1948

An earlier paper from these laboratories (1) reported the preparation of a series of α-stilbazole methiodides by the condensation of aromatic aldehydes with α-picoline methiodide. A similar series of compounds has now been made from γ-picoline methiodide. These compounds were made primarily for testing in a search for substances possessing curare-like activity. Incidental to the main purpose, certain correlations of possible theoretical interest have been noted in this and the earlier publication.

EXPERIMENTAL

All melting points are uncorrected.

Preparation of the γ-stilbazole methiodides. The general method of preparation is the same as that described for the α-stilbazole methiodides (1).

γ-Picoline methiodide, 5 g. (0.021 *M*), and 5 g. (0.03–0.04 *M*) of the aldehyde to be condensed were mixed and dissolved in 30 cc. of methanol. Piperidine (1 cc.) was added and the reaction mixture was refluxed on the steam-bath for a period of from one to four hours. After cooling, the solid was collected, washed with and recrystallized from methanol. Yields reported are in most cases those obtained after a single recrystallization from methanol of the first and second (obtained by partial evaporation of the original mother liquors) crops. Results are compiled in Table I.

Acknowledgment. The microanalytical results included were obtained by Mr. Samuel W. Blackman and absorption spectra were obtained by Miss Gertrude Elion. Their help is much appreciated.

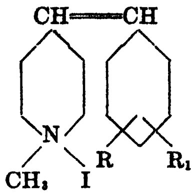
DISCUSSION

The compounds presented here manifest the same general relationship between color, yields obtained, and resonance possibilities of the products which was described previously for the α-series (1). Corresponding compounds from the two series were of about the same color.

With the highly colored members, the 4′-dialkylaminostilbazole methiodides, the γ-isomers appeared to be of a slightly deeper shade than their α-isomers. This observation, questionable as applied to visual examination of the solid substances, was supported by absorption spectra, for compound XIX (see Table I) had its characteristic maximum in the visible at 4540 Å [Clemo and Swan (2) reported a maximum at 4800 Å for this substance] as compared with 4440 Å for the α-isomer. Similarly the 4′-hydroxystilbazole methiodide, compound XI (Table I), which is highly colored in alkaline solution, had its maximum at 4450 Å in alkali as compared with 4350 Å for its α-analog in the same medium. Even in neutral medium a significant difference in the position of the maxima is observed for these two compounds: XI, 3750 Å; its α-analog, 3630 Å.

TABLE I

DERIVATIVES OF γ-STILBAZOLE METHIODIDE



COMP'D. NO.	SUBSTITUENTS ON BENZENE RING	M.P., °C.	YIELD %	ANALYSIS				ABSORPTION MAXIMUM, Å
				Calc'd		Found		
				C	H	C	H	
I	None	220–221	82	52.00	4.37	52.12	4.39	3350[a]
II	4-CH_3—	235–236	75	53.40	4.78	53.22	4.69	
III	2-Cl—	218–219	65	46.98	3.66	47.19	3.95	
IV	4-Cl—	250–251	70	46.98	3.66	46.95	3.63	
V	3-NO_2—[b]	>290	90	45.64	3.56	45.73	3.72	
VI	4-NO_2—	235–236	68	45.64	3.56	45.29	3.59	
VII	2-CH_3O—	194–195	94	50.98	4.57	51.15	4.42	
VIII	4-CH_3O—	214–215	98	50.98	4.57	50.72	4.68	3680[a]
IX	2-HO—	218–219	78	49.54	4.16	49.82	4.32	3660[a] 4510[c]
X	3-HO—	260–261	90	49.54	4.16	49.47	4.14	3430[a] 3450[c]
XI	4-HO—	265–266	80	49.54	4.16	49.23	4.10	3750[a] 4450[c]
XII	3,4-CH_2O_2<	283–284	93	49.03	3.84	49.16	3.77	
XIII	3,4-$(CH_3O—)_2$	253–254	81	50.12	4.72	50.04	4.76	
XIV	2,5-$(CH_3O—)_2$	246–247	96	50.12	4.72	50.38	4.64	
XV	3-CH_3O-4-HO—	275–276	64	48.77	4.36	48.92	4.62	
XVI	3-C_2H_5O-4-HO—	258–259	80	50.12	4.72	50.20	4.54	
XVII	2-HO-3-CH_3O—	247–248	94	48.77	4.36	48.98	4.29	
XVIII	2-HO-3-C_2H_5O—	236–237	90	50.12	4.72	50.36	4.72	
XIX	4-$(CH_3)_2N$—[d]	258–259	100	52.43	5.24	52.65	5.44	4540[a] 3275[e]
XX	4-$(C_2H_5)_2N$—	221–222	100	54.79	5.88	54.52	6.14	4710[a] 3310[e]
XXI	α-Furyl[f]	202–203	46	45.99	3.86	46.04	4.10	
XXII	α-Thienyl[f]	232–233	68	43.76	3.68	43.85	3.78	

[a] Absorption spectrum of a solution in distilled water.

[b] Crystallized from hot water.

[c] Absorption spectrum in aqueous sodium hydroxide.

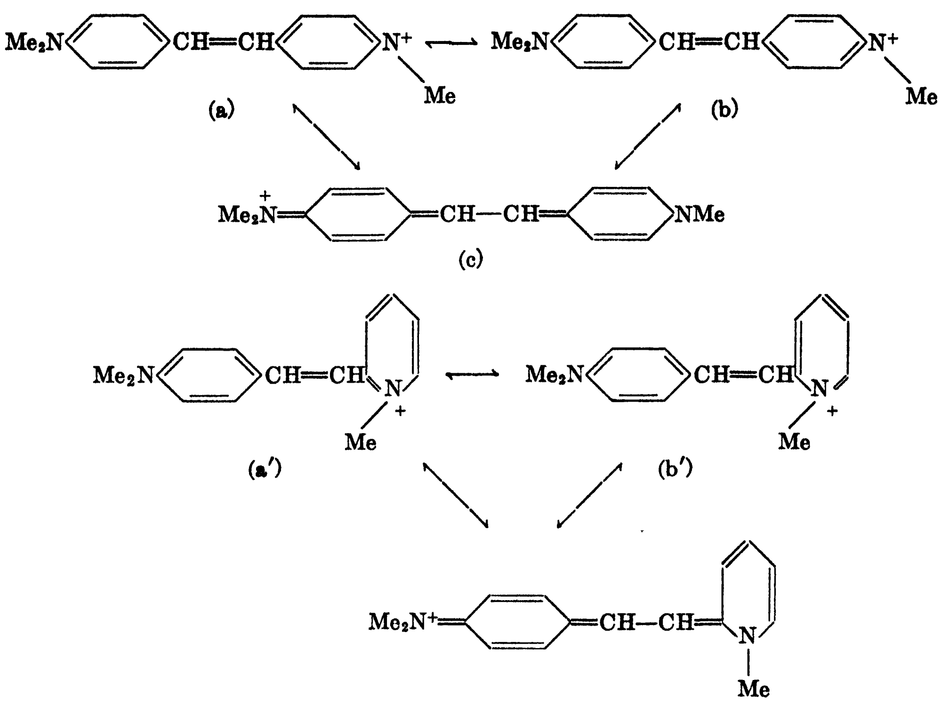
[d] Previously described by Clemo and Swan, reference (2).

[e] Absorption spectrum in aqueous hydrochloric acid.

[f] This ring in place of phenyl above.

With less highly colored compounds, where the resonance contribution of the styryl side chain would be expected to be of relatively lesser importance, the absorption maxima for the two analogous series show remarkably close agreement. Compound I (Table I), the simple styryl derivative, has its maximum at 3350 Å, its α-isomer at 3340 Å.

The significantly deeper color, absorption maxima at longer wave lengths, of the highly colored members of the γ-stilbazole methiodide group, as compared with the corresponding members of the α-group can probably be accounted for in



(c′)

FIG. 1

terms of a more favorable resonance situation in the γ compounds, as indicated in Fig. 1.

By use of the principal resonance variants shown in Fig. 1, the deeper color for the γ-isomer could reasonably be attributed to one or the other, or both, of two effects: 1. the variants for the γ-series (a, b, c) would afford an average longer chain of conjugated double bonds (mobile electronic system) since each possesses five conjugated double bonds between the cationic and tertiary nitrogens. On the other hand, in the α-system (a′, b′, c′) a′ has four double bonds between nitrogens, b′ has six, while c′ could be counted as either four or six, but with the possibility of the shorter route there seems no reason for weighing the longer

route as more important; 2. the energy contents of a and b would be identical, with c differing by some small amount. In contrast a′, b′, and c′ should all be of different energy and as a result resonance in the former groups of variants would be expected to be more favorable.

3′-Hydroxy-γ-stilbazole methiodide had absorption maxima for neutral and alkaline media at 3430 Å and 3450 Å, respectively, again confirming the visually observed and theoretically predicted result, equally applicable to either α or γ series, of no appreciable color change between the two media.

A number of aldehydes seemed to give significantly greater yields of condensation product with γ-picoline methiodide than they had with α-picoline methiodide. In spite of earlier reports (3) of the greater reactivity of the α-methylpyridines and quinolines (as compared to the γ-analogs) this observation is in accord with theory as interpreted earlier in this paper to explain the deeper color of the γ-isomers, and in the earlier paper (1) describing the relationships between structure and yields. However, a careful check has revealed that although this observation is doubtless correct in several cases, a more careful control of reaction time, ratio of reactants, and a modification of the method of isolating products is desirable to obtain more comparable results. These results, for a few selected aldehydes, will be presented in the near future.

SUMMARY

In the preparation of a series of γ-stilbazole methiodides the same general relationship between color, yields and resonance possibilities of the products has been observed as was reported previously for the α-isomers.

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[Contribution from the Institute of Organic Chemistry of the University of Szeged]

SYNTHESIS OF 1-(3,4-DIHYDROXYPHENYL)-1-AMINO-2-PROPANOL

J. KOVÁCS and T. HORVÁTH

Received November 8, 1948

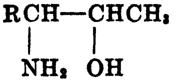
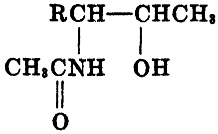
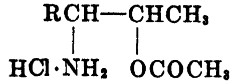
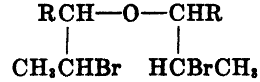
The present paper describes the synthesis of 1-(3,4-dihydroxyphenyl)-1-amino-2-propanol (VI), which is isomeric with the pharmacologically very active 1-(3,4-dihydroxyphenyl)-2-amino-1-propanol (VIII) (1). It was desired to obtain information concerning the connection between the structural change and the change in activity. According to the animal experiments, the 1-(3,4-dihydroxyphenyl)-1-amino-2-propanol loses its blood pressure activity through the change of position of the amino and alcoholic hydroxyl groups.

Synthesizing 1-(3,4-dihydroxyphenyl)-1-amino-2-propanol (VI), we started from 3,4-dibenzyloxypropenylbenzene (I), which is readily obtained from safrol in the manner described by Bruckner and Fodor (1) in their "corbasil" synthesis. The two benzyl groups can be easily eliminated by hydrogenolysis.

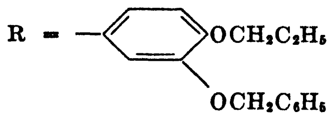
One can obtain from 3,4-dibenzyloxypropenylbenzene the suitable dibromo derivative (II). This can be converted nearly quantitatively into the corresponding bromohydrin (III) in a manner long known in the literature (2). The bromohydrin can be converted *via* an ethylene oxide derivative (IV) with methanolic ammonia at 150° into the amino alcohol (V). Passage through an intermediate product of the reaction is proved by the fact that the ethylene oxide derivative (IV)—obtained from the bromohydrin (III) with methanolic potassium hydroxide—can be converted with methanolic ammonia into the same amino alcohol (V).

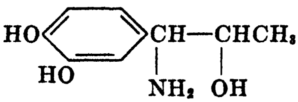
Theoretically the reaction can proceed in two directions, *i.e.*, 1-(3,4-dibenzyloxyphenyl)-2-amino-1-propanol or 1-(3,4-dibenzyloxyphenyl)-1-amino-2-propanol, and of course each has 2 racemic forms. However we succeeded in isolating, besides an oily reaction product, only the hydrobromide salt of 1-(3,4-dibenzyloxyphenyl)-1-amino-2-propanol (V) of one of the four racemates as the main product. Comparison of the melting point of the hydrochloride of 1-(3,4-dibenzyloxyphenyl)-1-amino-2-propanol (m.p. 189°) with that of the hydrochloride of 1-(3,4-dibenzyloxyphenyl)-2-amino-1-propanol prepared by Bruckner and Fodor (1) (m.p. 169°), does not prove decisively whether the amino and alcoholic hydroxyl groups are arranged according to formula (V), or formula (VIII). As formula (VIII) represents both of the stereoisomer types norephedrine and psi-norephedrine, the above mentioned difference of the melting points can also be explained by assuming the formation of both stereoisomers depending upon the synthesis employed.

I	II	III	IV
$RCH{=}CHCH_3$	$RCH(Br){-}CH(Br)CH_3$	$RCH(OH){-}CH(Br)CH_3$	$RCH{-}CHCH_3$ (bridged by O)

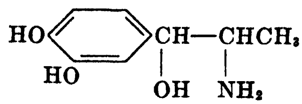





V IX X VII





VI



VIII

We decided the question through acetylation with acetic anhydride in pyridine, and obtained the N-acetylamino compound (IX), m.p. 131°. The compound was treated in the customary manner with phosphorus trichloride in toluene (3); if the arrangement of the hydroxyl and amino groups is as in VIII, we should have obtained the isoquinoline compound, as in the case of 1-(3,4-dibenzyloxyphenyl)-2-acetylamino-1-propanol (m.p. 113°) which under the same conditions cyclizes to 1,3-dimethyl-6,7-dibenzyloxyisoquinoline. Instead of this however a N → O acyl migration took place, and we isolated the hydrochloride of 1-(3,4-dibenzyloxyphenyl)-1-amino-2-propanol acetate (X) (m.p. 174°) from the reaction mixture.

On catalytic debenzylation of the amino alcohol (V) we obtained an amorphous, colorless, hygroscopic residue, which could not be crystallized, as in the case of the isomer corbasil (1). For the pharmacological investigations this amorphous compound (VI) was used.

We wish to add that the bromohydrin (III) must not be kept for long, because on standing, through condensation, an ether (VII) is formed.

EXPERIMENTAL

1-(3,4-Dibenzyloxyphenyl)-1,2-dibromopropane (II). Thirty-three and four-tenths grams of I was dissolved in 100 ml. of abs. chloroform and with cooling 16 g. of bromine in 20 ml. of chloroform was added dropwise. The pale yellow solution was evaporated under reduced pressure, and the crystalline residue was recrystallized from petroleum ether; long needles, m.p. 116°, yield, 40 g. The compound decomposed in light.

Anal. Calc'd for $C_{23}H_{22}Br_2O_2$: C, 56.32; H, 4.8.

Found: C, 56.7; H, 4.8.

1-(3,4-Dibenzyloxyphenyl)-2-bromo-1-propanol (III). Ten grams of II was dissolved in a mixture of 72 ml. of acetone and 18 ml. of water; 1.1 g. of $CaCO_3$ prec. was added, and the solution was warmed for an hour on the steam-bath. The homogeneous pale green solution was evaporated under reduced pressure at 50°. The oily residue was dissolved in ether, shaken with water, and dried with sodium sulfate. The ether yielded a nearly colorless dense oil, yield 7.8 g. This was dried under reduced pressure for a long time before analysis.

Anal. Calc'd for $C_{23}H_{23}BrO_3$: C, 64.7; H, 5.4.

Found: C, 65.2; H, 5.7.

1-(3,4-Dibenzyloxyphenyl)-2-methylethylene oxide (IV). Three and two-tenths grams of bromohydrin (III) was dissolved in 5 ml. of abs. methanol, and 0.45 g. of potassium hydroxide in 10 ml. of abs. alcohol was added to the solution. The potassium bromide separated immediately. After boiling for an hour the reaction mixture was evaporated and the oily residue dissolved in 20 ml. of abs. ether and kept in a desiccator over sulfuric acid and paraffin. The crystallization began soon and the colorless prisms were recrystallized from petroleum ether; m.p. 56°, yield 1.8 g.

Anal. Calc'd for $C_{23}H_{22}O_3$: C, 79.8; H, 6.4.
Found: C, 80.3; H, 6.5.

1-(3,4-Dibenzyloxyphenyl)-1-amino-2-propanol (V). Six grams of 1-(3,4-dibenzyloxyphenyl)-2-bromo-1-propanol (III) was dissolved in 48 ml. of abs. methanol containing 16% ammonia, and heated in a sealed tube for eleven hours at 150°. The pale green solution was evaporated and the oily residue was treated a few times with a small amount of ether. White crystals of the hydrobromide of amino alcohol V were obtained, yield 3.5 g. It was dissolved in alcohol and ether was added to turbidity; the solution soon deposited long needles, m.p. 194°.

Anal. Calc'd for $C_{23}H_{26}BrNO_3$: C, 62.2; H, 5.9.
Found: C, 62.6; H, 6.1.

The free base. Two-tenths gram of the hydrobromide of (V) was dissolved in a mixture of 27 ml. of water and 3 ml. of alcohol and treated to slight alkalinity with 5 *N* sodium hydroxide. An oil soon separated which crystallized in 24 hours. After recrystallization from dil. alcohol long needles were obtained, m.p. 85°.

Anal. Calc'd for $C_{23}H_{25}NO_3$: C, 76.0; H, 6.9.
Found: C, 76.0; H, 7.1.

The amino alcohol (V) prepared above, was dissolved in alcoholic HCl; the *hydrochloride of V* separated soon. It crystallized from a mixture of alcohol and ether in long needles, m.p. 189°.

Nine-tenths gram of IV was dissolved in 12 ml. of methanol containing 19% ammonia and heated in a sealed tube for ten hours at 105°. The pale green solution evaporated *in vacuo* to give a dense, oily residue which was dissolved in 30 ml. of dil. hydrochloric acid. It was shaken with ether a few times and treated with sodium hydroxide to alkalinity. The separated amine (V) crystallized in a yield of 0.4 g. It was converted to hydrochloride in the manner described above, m.p. 189°, not depressed in mixture.

1-(3,4-Dihydroxyphenyl)-1-amino-2-propanol hydrobromide (VI). Five-tenths gram of hydrobromide of V dissolved in 8 ml. of abs. methanol with 0.1 g. of previously hydrogenated 22% Pd charcoal absorbed the theoretical volume of hydrogen; the catalyst-free solution was evaporated at 30° in a hydrogen atmosphere. After the complete removal of the solvent and the toluene there remained a colorless foam. After thorough drying in a desiccator it weighed 0.3 g. (calc'd 0.297 g.). The very hygroscopic, oxidable compound could not be crystallized. It was used for the animal experiments.

1-(3,4-Dibenzyloxyphenyl)-1-acetylamino-2-propanol (IX). Six-tenths gram of 1-(3,4-dibenzyloxyphenyl)-1-amino-2-propanol (V) was dissolved in 3 ml. of abs. pyridine and 0.2 g. of acetic anhydride added under cooling. After standing overnight, it was diluted with 30 ml. of water. The oily acetylated compound separated, and crystallized on standing; this was triturated with dil. sulfuric acid and washed well with water. It crystallized in needles from dilute methanol, (50% water), m.p. 131°, yield 0.6 g.

Anal. Calc'd for $C_{25}H_{27}NO_4$: C, 74.1; H, 6.7.
Found: C, 74.4; H, 6.8.

1-(3,4-Dibenzyloxyphenyl)-1-amino-2-propanol acetate hydrochloride (X). Five-tenths gram of IX was dissolved in 5 ml. of abs. toluene, and after adding 0.5 ml. of phosphorus oxychloride the mixture was boiled one-half hour. On cooling, an oily product separated. The toluene was removed and shaken three times with 5 ml. of water. This aqueous solution was added to the oily product, which crystallized after 24 hours and was washed with ice cold water. It can be crystallized from alcohol-ether in long needles, m.p. 174°, yield 0.24 g.

Anal. Calc'd for $C_{25}H_{28}ClNO_4$: C, 67.9; H, 6.4.
Found: C, 67.7; H, 6.4.

Di-[1,1'-(3,4-dibenzyloxyphenyl)-2,2'-dibromopropyl] ether (VII). 1-(3,4-Dibenzyloxyphenyl)-2-bromo-1-propanol (III), after standing for 10–12 days, was treated with methanol, and became crystalline. After washing with methanol it was crystallized from alcohol or acetone, m.p. 108°.

Anal. Calc'd for $C_{46}H_{44}Br_2O_5$: C, 66.0; H, 5.3.
Found: C, 66.2; H. 5.4.

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[Contribution from the Department of Chemistry of Duke University]

SUBSTITUTIONS AT THE α- OR γ-POSITIONS IN PYRIDYL RING SYSTEMS BY BASIC REAGENTS[1]

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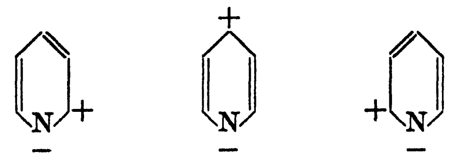
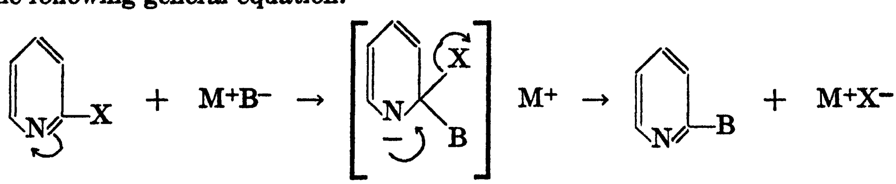
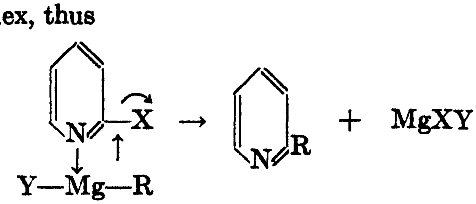
Pyridine may exhibit certain typical aromatic substitutions of the electrophilic type such as bromination and nitration to form the β-derivative, but these reactions take place with some difficulty. Pyridine and especially α- or γ-halopyridines have a greater tendency to undergo nucleophilic substitutions with certain basic reagents to form the α- or γ-derivative. This is not surprising since the following ionic resonance structures having positive charges at the α or γ positions appear to make significant contributions to the structure of the molecule (1, 2).



In contrast to electrophilic substitutions in which hydrogen is removed as a proton, nucleophilic substitutions involve the displacement of hydride (2) or halide ion (3). In certain cases methoxide ion or the sulfonic acid group may be displaced (4). As might be expected, halide ion may be displaced by certain bases which are too weak to displace hydride ion; even with certain relatively strong bases, it is sometimes expedient to facilitate the displacement of hydride ion by the presence of oxidizing agents (2). The mechanism of the displacement of X^- (hydride ion, halide ion, etc.) by a basic anion, B^-, may be represented by the following general equation.



It is not clear whether the addition complex is actually formed (5) or whether X^- is displaced directly from the pyridine ring system (2). With Grignard reagents or organolithium compounds the displacement may take place within a coordination complex, thus



[1] Part of this work was supported by a grant from the Duke University Research Council.
[2] Eli Lilly Fellow, 1947–1948.

Displacements of hydride ion. Hydride ion may be displaced from pyridyl ring systems by amide ion (5). Generally the 2-amino derivative is formed. With pyridine, for example, 2-aminopyridine is produced, the product being converted in the reaction mixture to its anion.

Although this reaction with alkali amides is quite general, the corresponding reaction with metallic derivatives of amines has seldom been realized. Bergstrom and co-workers (6) have introduced certain primary aliphatic amine groups into pyridine rings under special conditions, but the reaction has failed with secondary aliphatic amines or aniline. Chichibabin and Seide (7) reported only a slight yield of 2-anilinopyridine from sodium anilide and pyridine. We have been unable to effect the reaction with sodium methylanilide and pyridine, with diethylaminomagnesium bromide and quinoline, or with lithium dibutylamide and pyridine or quinoline.

Hydride ion may be displaced even by hydroxide ion but a relatively high temperature appears to be required. Thus, quinoline and potassium hydroxide react at about 300° to form 2-hydroxyquinoline and hydrogen (8).

Hydride ion may be substituted by the potential carbanions of Grignard reagents and organolithium compounds such as phenylmagnesium bromide (8) and phenyllithium (8). Thus, with pyridine and phenyllithium, 2-phenylpyridine is formed. However, Bergmann and Rosenthal (9) were unable to condense sodium diphenylmethide with pyridine, quinoline, or isoquinoline, although they did realize condensation with acridine. We have been unable to condense potassium diphenylmethide or potassium quinaldide with pyridine.

Displacements of halide ion. Halogen at the α- or γ-position of pyridyl ring systems may be displaced as halide ion by various basic reagents including hydroxide ion, phenoxide ion, ethoxide ion, and even ammonia and primary and secondary amines (10). Also Gilman and co-workers (11) have displaced halide ion from 2-chloroquinoline with lithium diethylamide. However, earlier workers (12) failed to obtain the 2-amino derivative from 2-bromopyridine or 2-chloroquinoline and potassium amide.

We have effected this type of reaction not only with sodium and potassium amide but also with sodium methylanilide, di-*n*-butylaminomagnesium bromide, and certain related basic reagents. Our results are summarized in Table I. The yields are not necessarily the optimum obtainable. Sodium methylanilide and similar reagents were prepared from sodium amide and the appropriate aromatic amine.

$$C_6H_5NHCH_3 + NaNH_2 \rightarrow C_6H_5N(Na)CH_3 + NH_3$$

Di-*n*-butylaminomagnesium bromide and other magnesium derivatives were prepared from standardized ethylmagnesium bromide solution and the appropriate aromatic or aliphatic amine (13).

$$C_2H_5MgBr + (n\text{—}C_4H_9)_2NH \rightarrow (n\text{—}C_4H_9)_2NMgBr + C_2H_6$$

In general the reactions between the alkali amides and the halogen compounds were first carried out in liquid ammonia or in liquid ammonia followed by reflux-

TABLE I

Results with Basic Reagents and 2-Bromopyridine (2-BrP), 2-Chloroquinoline (2-ClQ), and 4,7-Dichloroquinoline (DCQ)

Halogen compound	Moles	Basic reagent	Moles	Solvent (reflux temp.)	Time (hrs.)	Product	B.P., °C	mm.	Yield (%)
2-BrP	.06	$NaNH_2$	.12	Liq. NH_3	4	2-Aminopyridine	120–121[a]	36.5	67
2-BrP	.03	KNH_2	.06	Liq. NH_3	6	2-Aminopyridine	118–120[a]	36	77
							55–57[b] (m.p.)		
2-BrP	.06	KNH_2	.12	Liq. NH_3	0.5	2-Aminopyridine	54–57[b] (m.p.)		49
2-ClQ	.06	$NaNH_2$	.15	Liq. NH_3	5	2-Aminoquinoline	127–128[c] (m.p.)		22
2-ClQ	.06	KNH_2	.15	Liq. NH_3	4	2-Aminoquinoline	123[c] (m.p.)		15
				Ethyl ether	12[d]				
2-ClQ	.025	C_6H_5NHNa	.05	Liq. NH_3	3	2-Anilinoquinoline	93–96 (m.p.)		20
				Ethyl ether	12	Di-α-quinolylphenylamine	200 *ca.* (m.p.)		20
2-ClQ	.025	$C_6H_5NHMgBr$	.05	Butyl ether	12	2-Anilinoquinoline	96–97 (m.p.)		28(43)[e]
2-BrP	.10	$C_6H_5\overset{\overset{CH_3}{\vert}}{N}Na$	.10	Liq. NH_3	1.5	2-Methylanilinopyridine	147–148	10	57(62)[e]
				Ethyl ether	2				
2-ClQ	.06	$C_6H_5\overset{\overset{CH_3}{\vert}}{N}Na$	.07	Liq. NH_3	1.5	2-Methylanilinoquinoline	165–175	1.5	47
				Ethyl ether	4				
2-ClQ	.09	$C_6H_5\overset{\overset{CH_3}{\vert}}{N}MgBr$	.10	Ethyl ether	6 + 12[d]	2-Methylanilinoquinoline	172–182	3	43(61)[e]
DCQ	.05	$C_6H_5\overset{\overset{CH_3}{\vert}}{N}Na$	.05	Liq. NH_3	4	7-Chloro-4-methylanilinoquinoline	194–205	1	46
				Ethyl ether	10[d]				
2-BrP	.045	$(C_6H_5)_2NNa$	.06	Butyl ether[f]	3	2-Diphenylaminopyridine	95–99 (m.p.)		17

2-ClQ	.025	n-$C_4H_9NHMgBr$	.05	Butyl ether[g]	20	Di - α - quinolyl - n - butylamine	90–92 (m.p.)		54
2-ClQ	.10	$(n$-$C_4H_9)_2NMgBr$	.11	Ethyl ether	6 + 10[d]	2 - Di - n - butylamino-quinoline	168–169	1.5	48(60)[e]
DCQ	.045	$(n$-$C_4H_9)_2NMgBr$	.10	Butyl ether[h]	12	7 - Chloro - 4 - di - n - butylaminoquinoline	185 *ca.*	7	3
2-BrP	.05	$(n$-$C_4H_9)_2NMgBr$	.05	Ethyl ether	12	2 - Di - n - butylamino-pyridine	155[i]	20	11(19)[e]
2-ClQ	.09	C_6H_5MgBr	.09	Ethyl ether	9	2-Phenylquinoline	82.5–83 (m.p.)		40

[a] Ref. 26 reports 117–120° at 36 mm.

[b] Lange (Handbook of Chemistry, 3rd edition, 1939, p. 279) lists 56°.

[c] Footnote b lists 129°.

[d] At room temperature.

[e] Yield is based on halogen compound used minus that recovered.

[f] When the reaction was carried out in liquid ammonia for one hour and in refluxing ethyl ether for four hours, 61% of the 2-BrP was recovered.

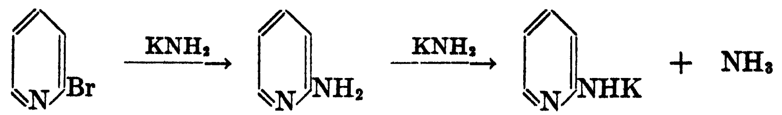
[g] When the reaction was carried out in ethyl ether for fourteen hours, 81% of the 2-ClQ was recovered.

[h] When the reaction between equimolecular amounts was carried out in ethyl ether for ten hours at reflux and for thirty-six hours at room temperature, 80%, of the DCQ was recovered.

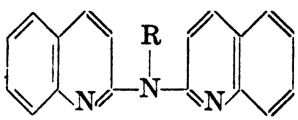
[i] Reported b.p. 163° at 20 mm. (22).

ing diethyl ether; if the reaction failed under these conditions it was repeated in refluxing di-n-butyl ether. The reactions with the magnesium derivatives were usually carried out first in refluxing diethyl ether, and if the reaction failed it was repeated in refluxing di-n-butyl ether.

It can be seen from Table I that, with sodium or potassium amide in liquid ammonia, 2-bromopyridine gave a good yield of 2-aminopyridine but that a considerably lower yield of 2-aminoquinoline was obtained from 2-chloroquinoline.



With sodium anilide or anilinomagnesium bromide and 2-chloroquinoline a fair yield of 2-anilinoquinoline was obtained. With the sodium anilide another compound, apparently the disubstituted product (I, R = C_6H_5), also was formed.



(I)

With sodium methylanilide, 2-bromopyridine, 2-chloroquinoline and 4,7-dichloroquinoline gave fair to good yields of 2-methylanilinopyridine, 2-methylanilinoquinoline and 7-chloro-4-methylanilinoquinoline, respectively. A fairly good yield of 2-methylanilinoquinoline was also obtained from 2-chloroquinoline and methylanilinomagnesium bromide. With sodium diphenylamide in refluxing di-n-butyl ether, 2-bromopyridine gave a 17% yield of 2-diphenylaminopyridine.

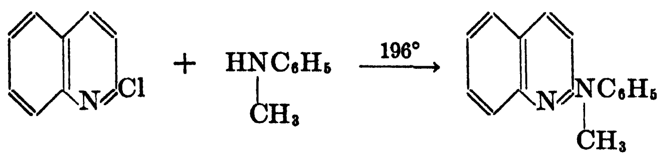
Since aliphatic amines are not readily converted to alkali metal amides, only the bromomagnesium derivatives of these amines were used. With n-butylaminomagnesium bromide in refluxing di-n-butyl ether, 2-chloroquinoline gave the di-substituted product (I, R = n-C_4H_9). The reaction failed in ethyl ether. With di-n-butylaminomagnesium bromide, 2-chloroquinoline gave a satisfactory yield of 2-di-n-butylaminoquinoline but 2-bromopyridine and 4,7-dichloroquinoline failed to give satisfactory yields.

With the potential carbanion of phenylmagnesium bromide, 2-chloroquinoline gave 2-phenylquinoline in 40% yield. Walter and McElvain (14) have condensed sodio-ethylmalonic ester with 2-bromopyridine to form ethyl-2-pyridylmalonic ester. However, we have been unable to condense satisfactorily the sodium salts of ethyl isobutyrate (15), acetone[3] (16) and methyl isobutyl ketone (16) with 2-bromopyridine. Potassium diphenylmethide (17) also failed to condense with 2-bromopyridine. It is of interest that when this reaction was carried out in liquid ammonia, 2-aminopyridine was obtained in 64% yield, which is approximately the same yield obtained with potassium amide alone. Apparently the amide ion, which is in equilibrium with the diphenylmethide ion, reacted

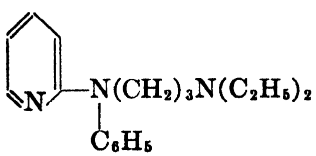
[3] Unsuccessful attempts have been made to condense acetone with 2-bromo-pyridine in the presence of boron trifluoride.

much more rapidly with the 2-bromopyridine than did the relatively large diphenylmethide ion. Similarly, with potassium diphenylmethide and 2-chloroquinoline, 2-aminoquinoline was obtained, although the yield was only 11%.

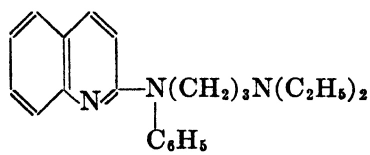
As it has been pointed out above, even free primary and secondary amines may be coupled with α- or γ-halopyridyl compounds, although the reaction generally appears to require higher temperatures. Actually, this reaction is used in the synthesis of the well known antimalarials, quinacrine and SN 7618; the latter is obtained by coupling 4-diethylamino-1-aminopentane with 4,7-dichloroquinoline at 160–170° (18). Since an example with a secondary aromatic amine could not be found in the literature, we have coupled methylaniline with 2-chloroquinoline; the product was obtained in 87% yield which is considerably higher than the yields with the metallic derivatives of methylaniline (see Table I).



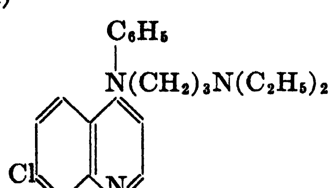
In connection with this study, it seemed of interest to synthesize compounds (II), (III), and (IV), which are somewhat related to the well known antimalarials, quinacrine and SN 7618.



(II)



(III)



(IV)

Compounds (II) and (IV) were prepared by reacting the potassium salt of the diamine, N-(γ-diethylaminopropyl)aniline (V), with 2-bromopyridine and 4,7-dichloroquinoline, respectively. Compound (III) was obtained from the magnesium derivative of the diamine and 2-chloroquinoline. The diamine was prepared from aniline by the following series of reactions.

$$C_6H_5NH_2 + p\text{-}CH_3C_6H_4SO_2Cl \rightarrow C_6H_5NHSO_2C_6H_4CH_3\text{-}p \xrightarrow[+\ K_2CO_3]{Cl(CH_2)_3N(C_2H_5)_2}$$

$$\underset{\displaystyle CH_2CH_2CH_2N(C_2H_5)_2}{C_6H_5NSO_2C_6H_4CH_3\text{-}p} \xrightarrow{HCl} \underset{(V)}{C_6H_5NHCH_2CH_2CH_2N(C_2H_5)_2}$$

The direct condensation of γ-diethylaminopropyl chloride with aniline gave a mixture which consisted presumably of the mono- and the di-alkylated products.

2-Methylanilinoquinoline, 2-di-*n*-butylaminoquinoline, and compounds (II), (III), and (IV) were tested as potential antimalarials at the Lilly Research Laboratories of Eli Lilly and Company, Indianapolis, Indiana. The tests were carried out in ducks infected with *P. lophurae*. The compounds were, however, all inactive. Four of these compounds were also tested for activity against tuberculosis. The tuberculosis tests were carried out *in vitro* using avirulent human strain No. 599. 2-Methylanilinoquinoline showed activity at a minimum dosage of 0.2 mg. per 10 ml. of culture. Compounds (III) and (IV) were active at a minimum dosage of 2 mg., and compound (II) was active at a minimum dosage of 20 mg.

EXPERIMENTAL[4,5]

Halogen compounds. 4,7-Dichloroquinoline (m.p. 86–87°) and 2-chloroquinoline (b.p. 152–154° at 22 mm.) were commercial products. 2-Bromopyridine (b.p. 88–89° at 24 mm.) was prepared in 85% yield from 200 g. of 2-aminopyridine and the corresponding amounts of sodium nitrite, bromine and 48% hydrobromic acid essentially by the method of Craig (19).

Preparation of metallic bases. Sodium or potassium amide was made in the usual manner (16, 17) in a three-necked flask (ground glass joints) fitted with a mercury-sealed stirrer, dropping-funnel, and a condenser having an attached Drierite drying tube. Sodium anilide and sodium methylanilide were prepared by the addition of the redistilled amine, dissolved in an equal volume of anhydrous ether, to an equivalent of sodium amide suspended in liquid ammonia. The anilide and the methylanilide, which were both soluble in liquid ammonia, were formed almost immediately.

Sodium diphenylamide was prepared in a similar manner except that, after all the diphenylamine (m.p. 54°) had been added, the ammonia was replaced by anhydrous di-*n*-butyl ether (b.p. 141°) and the suspension stirred and refluxed for two hours to ensure complete conversion to the salt.

The magnesium bases were prepared using the apparatus described above, by the dropwise addition of an equivalent of the redistilled amine, dissolved in anhydrous ether, to a stirred 0.2 molar solution of ethylmagnesium bromide (13). The reaction was considered complete after twenty to thirty minutes. Di-*n*-butylaminomagnesium bromide, *n*-butylaminomagnesium bromide, and methylanilinomagnesium bromide were all soluble in ether. Anilinomagnesium bromide was insoluble in ether.

Reactions of halogen compounds with metallic bases. The proportions of reactants, the general conditions, the yields and the physical constants of the products are summarized in Table I. The procedures with the various metallic bases are described below.

(A). *With sodium or potassium amide.* A solution of 2-bromopyridine or 2-chloroquinoline in an equal volume of anhydrous ether was added dropwise to a liquid ammonia suspension of sodium amide or a solution of potassium amide and the reaction mixture was allowed to reflux (a Dry-Ice reflux condenser with attached Drierite tube was used). The salts were decomposed by the careful addition of excess solid ammonium chloride. The ammonia was allowed to evaporate and about 50 ml. of 5% sodium hydroxide solution for each 0.1 mole of amide ion used was then carefully added.

2-Aminopyridine was isolated by saturating the sodium hydroxide solution with sodium hydroxide pellets in an ice-bath, followed by extraction with ether. After drying over Drierite the ether was removed and the residue was distilled *in vacuo*; usually there was no forerun.

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[4] Analyses were done by Oakwold Laboratories, Alexandria, Va.

[5] Boiling points are uncorrected; melting points, unless otherwise stated, are also uncorrected.

2-Aminoquinoline was isolated from the tar, which was formed after the alkali treatment, by several extractions with boiling distilled water. The water solution was evaporated to about 75 ml., treated with Norit, and chilled to give fine white crystals.

(B). *With sodium anilide.* To a stirred solution of sodium anilide in liquid ammonia was added dropwise a solution of 2-chloroquinoline in anhydrous ether. Some heat was evolved and a black solid soon formed. After three hours the ammonia was replaced by ether and the ether was refluxed. Potassium carbonate solution was then added, producing a red solid, and the mixture was extracted several times with ether. The portion of the solid which did not dissolve in ether was suction-filtered, washed with water, and dried *in vacuo* (see below). The combined ether extracts were dried over anhydrous potassium carbonate and the solvent distilled. The residue was fractionated *in vacuo* through an eleven-cm. Vigreux column up to 81° at 21.5 mm., and the remainder distilled through a von Braun head, giving a 46% yield of crude 2-anilinoquinoline boiling at 200–205° at 3.5 mm. and melting at 75–87°. Two recrystallizations from ligroin (b.p. 70–90°) using Norit gave crystals (20% yield) melting at 93–96°; a third recrystallization raised the melting point to 96–98°; reported m.p. 98° (20).

The ether-insoluble material mentioned above, after several recrystallizations from ethyl acetate, melted at approximately 200°, a constant melting point being difficult to obtain. A sample analyzed for di-α-quinolylphenylamine (I, R = C_6H_5).

Anal. Calc'd for $C_{24}H_{17}N_3$: N, 12.10. Found: N, 11.88.

(C). *With sodium methylanilide.* The reactions of 2-bromopyridine, 2-chloroquinoline and 4,7-dichloroquinoline with this basic reagent were carried out as described above for sodium anilide. At the conclusion of the refluxing period the ether solution was decanted and the solid washed with anhydrous ether till the washings were practically colorless. The solvent was removed from the combined ether solutions and the residue was distilled *in vacuo* through an eleven-cm. Vigreux column.

2-Methylanilinopyridine was redistilled, b.p. 147° at 10 mm. and analyzed as the free base.

Anal. Calc'd for $C_{12}H_{12}N_2$: C, 78.22; H, 6.57; N, 15.21.

Found: C, 78.17; H, 6.23; N, 15.52.

2-Methylanilinoquinoline was converted to its hydrobromide salt by adding 34% hydro bromic acid to a solution of the free base in ether until no more white crystals formed. The crystals were suction-filtered, washed with a small amount of acetone and recrystallized from a mixture of 95% ethanol and isopropyl ether to give a product melting at 260° corr.

Anal. Calc'd for $C_{16}H_{14}N_2 \cdot HBr$: C, 60.96; H, 4.80; Br^-, 25.35; N, 8.89.

Found: C, 60.45; H, 4.69; Br^-, 25.41; N, 9.37.

7-Chloro-4-methylanilinoquinoline was obtained as a heavy red oil which crystallized after several days standing at room temperature. This compound (m.p. 68–73°) was converted to its monohydrochloride salt by passing hydrogen chloride gas through an ether solution of it, and recrystallizing the precipitated salt four times from a mixture of ethanol and ethyl acetate. The salt (pale orange yellow needles) melted at 192–193° corr. and analyzed as the monohydrate.

Anal. Calc'd for $C_{16}H_{13}ClN_2 \cdot HCl \cdot H_2O$: C, 59.45; H, 4.99; Cl^-, 10.97; N, 8.67.

Found: C, 59.58; H, 4.95; Cl^-, 10.88; N, 8.96.

(D). *With sodium diphenylamide.* 2-Bromopyridine was added to a stirred suspension of sodium diphenylamide in di-*n*-butyl ether and the reaction mixture was refluxed on a Wood's metal-bath. After cooling, the salts were decomposed with a few ml. of water and the butyl ether solution was then extracted several times with 6 *N* hydrochloric acid solution. The combined acid extracts after separation from a large amount of black solid were saturated with potassium carbonate, extracted several times with ether and the combined ether solutions were dried over anhydrous sodium sulfate. After the ether was removed, the residue was fractionated through an eleven-cm. Vigreux column at 6 mm. yielding two fractions, b.p. 152–193° (partially solid) and b.p. 193° (m.p. 83–93°). The combined fractions were recrystallized from ethanol-water (Norit) to give 2-diphenylaminopyridine as

white crystals melting at 95–99°. Further recrystallization raised the melting point to 102–103.5°; reported m.p. 104° (21).

(E). *With the magnesium bases.* To a solution or suspension of the magnesium base was added the halogen compound, dissolved in anhydrous ethyl ether, and the mixture refluxed. In certain cases the ethyl ether was replaced by di-*n*-butyl ether and the reaction mixture was then stirred and refluxed. An aqueous ammonium chloride solution was added slowly with stirring; the two layers were separated and the aqueous layer, after saturation with ammonium chloride, was thoroughly extracted with ether. In some cases solids or oils formed during the course of the reaction; these experiments were, however, worked up in the same way as the others.

In the experiments carried out in ethyl ether the combined ether extracts were dried over potassium carbonate, the ether was removed and the residue was distilled *in vacuo* through an eleven-cm. Vigreux column.

In the experiments carried out in di-*n*-butyl ether the combined ether extracts were extracted several times with 6 *N* hydrochloric acid solution. After the combined acid solutions were saturated with potassium carbonate, the mixture was extracted several times with ether. The combined ether solutions were dried, the solvent distilled and the residue fractionated.

Di-α-quinolyl-*n*-butylamine (I, R = $n-C_4H_9$) was obtained, after evaporation of the ether, as a red oil which solidified after several days in the refrigerator. One recrystallization from methanol-water gave white crystals melting at 90–92°. Two additional recrystallizations raised the melting point to 91–92°.

Anal. Calc'd for $C_{22}H_{21}N_3$: C, 80.70; H, 6.47; N, 12.83.
Found: C, 80.49; H, 6.10; N, 13.21.

The monopicrate after three recrystallizations from methyl isobutyl ketone melted at 181–182° corr.

Anal. Calc'd for $C_{28}H_{24}N_6O_7$: C, 60.43; H, 4.35; N, 15.10.
Found: C, 60.80; H, 4.37; N, 15.54.

2-Di-*n*-butylaminopyridine was characterized as the monopicrate, which after three recrystallizations from 95% ethanol melted partly at 130–132° and partly at 134–135°; reported m.p. 136–137° (22).

Anal. Calc'd for $C_{19}H_{25}N_5O_7$: C, 52.41; H, 5.79; N, 16.09.
Found: C, 52.14; H, 5.57; N, 16.12, 16.14.

2-Di-*n*-butylaminoquinoline was carefully redistilled through a fifteen-cm. Vigreux column and a mid-fraction boiling at 172–173° at 2.5 mm. was analyzed as the free base.

Anal. Calc'd for $C_{17}H_{24}N_2$: C, 79.63; H, 9.44; N, 10.93.
Found: C, 79.50; H, 9.33; N, 11.00.

7-Chloro-4-di-*n*-butylaminoquinoline was characterized as the monopicrate, which after four recrystallizations from ethanol-dioxane melted at 178–180° after much sintering.

Anal. Calc'd for $C_{23}H_{26}ClN_5O_7$: N, 13.47. Found: N, 13.29.

2-Anilinoquinoline was obtained crude in 40% yield (b.p. 207° at 4 mm.; m.p. 87–95°). One recrystallization from ligroin (b.p. 70–90°) gave a product (28% yield) melting at 96–97°; reported m.p. 98° (20).

2-Phenylquinoline was obtained from 2-chloroquinoline and phenylmagnesium bromide, which was prepared in the usual manner. The crude product (b.p. 172–182° at 3.5 mm., m.p. 71–75°) was obtained in 52% yield by distillation through an eleven-cm. Vigreux column. A fair amount of higher-boiling material was also present. Two recrystallizations of the crude product from a mixture of ethanol and water gave white crystals melting at 82.5–83° (23). Further recrystallization did not raise the melting point.

Reaction of 2-chloroquinoline with methylaniline. A solution of 9.2 g. (0.085 mole) of methylaniline and 7.0 g. (0.043 mole) of 2-chloroquinoline was refluxed for nine hours on a Wood's metal-bath maintained at 250°. The reaction mixture was allowed to cool and was then poured into potassium carbonate solution. After the combined ether extracts of this mixture had been dried over potassium carbonate, the ether was distilled and the residue

was fractionated through a fifteen-cm. Vigreux column to give 3.7 g. (40% recovery) of methylaniline and 8.8 g. (87% yield) of 2-methylanilinoquinoline (b.p. 204–214° at 10 mm.) A portion of this product was converted to the hydrobromide salt as described in (C). A mixed melting point of this salt with the salt obtained in (C) showed no depression.

Derivatives of N-(γ-diethylaminopropyl)aniline (V). *p*-Toluenesulfonanilide (m.p. 99–101°) was prepared in 96% yield from aniline and *p*-toluenesulfonylchloride in pyridine. The product after two recrystallizations from ethanol-water melted at 101°; reported m.p. 103° (24).

To a solution of 94 g. (0.38 mole) of *p*-toluenesulfonanilide (m.p. 99–101°) and 66.8 g. (0.45 mole) of γ-diethylaminopropyl chloride (25) in 325 ml. of commercial absolute ethanol was added 52.5 g. (0.38 mole) of anhydrous potassium carbonate. After the reaction mixture had been refluxed for seventeen hours, about 200 ml. of ethanol was distilled off, the residue was poured into 300 ml. of 6 *N* hydrochloric acid and the small amount of insoluble material was filtered off. The acid solution was made alkaline with sodium carbonate and the resulting mixture was thoroughly extracted with chloroform. The chloroform was distilled leaving crude N-(γ-diethylaminopropyl)-*p*-toluenesulfonanilide. This crude alkylated sulfonanilide was hydrolyzed as described below. It was isolated from a small scale experiment starting with 10 g. of *p*-toluenesulfonanilide in 78% yield as a viscous yellow oil boiling at 252–256° at 7.5 mm. The picrate melting at 144–145° corr. after recrystallization from a mixture of ethanol and dioxane was analyzed.

Anal. Calc'd for $C_{26}H_{31}N_5O_9S$: C, 52.96; H, 5.30; N, 11.88; S, 5.44.
Found: C, 52.60; H, 5 27; N, 11.72; S, 5.63.

The hydrolysis of the crude alkylated sulfonanilide was carried out by refluxing it for seventeen hours in 900 ml. of 20% hydrochloric acid. The solution was cooled, saturated with sodium carbonate, and extracted several times with ether. After drying the combined ether extracts over potassium carbonate, the ether was distilled and the residue was fractionated *in vacuo* through a fifteen-cm. Vigreux column, yielding, after a slight forerun, 44.8 g. (59% overall yield from aniline) of N-(γ-diethylaminopropyl)aniline as a colorless oil boiling at 160–161° at 12.5 mm. A portion of this product was carefully redistilled and a portion of the mid-fraction boiling at 156.5° at 11 mm. was submitted for analysis.

Anal. Calc'd for $C_{13}H_{22}N_2$: C, 75.67; H, 10.75; N, 13.58.
Found: C, 75.13; H, 10.69; N, 13.67.

γ-Diethylaminopropylphenyl-α-quinolylamine (III). An ethyl ether solution containing 4.1 g. (0.025 mole) of 2-chloroquinoline and N-(γ-diethylaminopropyl)anilinomagnesium bromide, prepared from 5.1 g. (0.025 mole) of the diamine, was refluxed for thirty hours and allowed to stand at room temperature for twelve hours. The reaction mixture was then worked up as described above in (E), except that the product was distilled from a 50-ml. Claisen distilling flask to give 4.2 g. (51% yield) of crude γ-diethylaminopropylphenyl-α-quinolylamine as a yellow oil boiling at 175–193° at 2 mm.

A similar experiment carried out by refluxing the reaction mixture for 120 hours gave only a 42% yield of product.

The product was converted to its dihydriodide salt by the addition of an excess of a 47% hydriodic acid solution to the free base dissolved in isopropyl alcohol. The alcohol solution was heated to reflux and isopropyl ether was added till the solution became cloudy. On cooling, an oil formed, which solidified after twenty-four hours in the refrigerator. Four recrystallizations from isopropyl alcohol gave pale yellow needles melting at 185–186° corr.

Anal. Calc'd for $C_{22}H_{27}N_3 \cdot 2HI$: I^-, 43.07; N, 7.13.
Found: I^-, 42.69; N, 7.51.

γ-Diethylaminopropylphenyl-α-pyridylamine (II). The potassium salt of N-(γ-diethylaminopropyl)aniline was prepared according to the general procedure described above for alkali metal salts. In order to ensure satisfactory conversion, the ammonia was replaced by anhydrous ethyl ether and the ether suspension was stirred and refluxed for six hours, nitrogen being passed over the mixture during the last three hours. To the ether suspension of this salt was added an equivalent of 2-bromopyridine (4.7 g.; 0.029 mole), dissolved

in anhydrous ether. The mixture was refluxed and stirred for twenty-eight hours and the reaction mixture was then worked up as in (C), except that the product was distilled from a 50-ml. Claisen flask, to give 3.1 g. of recovered N-(γ-diethylaminopropyl)aniline and 2.8 g. (35%) of γ-diethylaminopropylphenyl-α-pyridylamine as a red oil boiling at 185–195° at 5 mm.; the yield was 70% when based on the N-(γ-diethylaminopropyl)aniline used, minus that recovered. When this compound was prepared by the magnesium salt method with a reflux period of 120 hours the yield was only 21%; the yield was 35% when based on the 2-bromopyridine and the N-(γ-diethylaminopropyl)aniline used minus that recovered. The product was converted to its dihydriodide salt by the dropwise addition of a 64% hydriodic acid solution to an ether solution of the free base. The oil which first formed soon crystallized on standing in the refrigerator. The salt was recrystallized four times from a mixture of commercial absolute ethanol and isopropyl ether, yielding white crystals melting at 187–188.5° corr.

Anal. Calc'd for $C_{18}H_{25}N_3 \cdot 2HI$: C, 40.09; H, 5.05; I^-, 47.07; N, 7.79.
Found: C, 40.61; H, 5.01; I^-, 47.27; N, 7.88.

γ-Diethylaminopropylphenyl-(7-chloro-4-quinolyl)amine (IV). This compound (b.p. 228° at 3 mm.) was prepared in 47% yield from 4,7-dichloroquinoline and the potassium salt of N-(γ-diethylaminopropyl)aniline. The reaction mixture was stirred and refluxed for 96 hours.

The product was converted to its dihydriodide salt as described for the salt of (IV). Three recrystallizations from a mixture of commercial absolute ethanol and isopropyl ether gave orange crystals melting at 192.5–193° corr.

Anal. Calc'd for $C_{22}H_{26}ClN_3 \cdot 2HI$: I^-, 40.70; N, 6.74.
Found: I^-, 40.91; N, 6.83.

SUMMARY

The scope, limitations, and mechanism of nucleophilic substitutions in pyridyl ring systems have been considered. α- and γ-Halopyridyl rings have been substituted with sodium and potassium amide, sodium methylanilide, di-*n*-butylaminomagnesium bromide and certain related basic reagents. Methylaniline has been coupled with 2-chloroquinoline.

Certain potential antimalarials have been synthesized.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF STANFORD UNIVERSITY]

THE EQUILIBRIUM BETWEEN 2-AMINO- AND 2-ALKYLAMINO-QUINOLINES[1]

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It has been reported by Bergstrom *et al.* (1) that 2-alkylaminopyridines and 2-alkylaminoquinolines are obtained in fairly good yields by heating the eutectic mixture of sodium-potassium amide with pyridine or quinoline dissolved in a primary aliphatic amine. In this manner, for example, 2-cyclohexylaminoquinoline was obtained in 77% yield. A mechanism for this reaction was suggested:

$$\text{—CH═N— } + \text{ NH}_2^- \rightarrow \text{—CH(NH}_2\text{)—N}^{-}\text{—} \qquad \text{I}$$

$$\text{—CH(NH}_2\text{)N}^{-}\text{— } + \text{ RNH}_2 \leftrightarrows \text{—CH(NHR)—N}^{-}\text{— } + \text{ NH}_3 \qquad \text{II}$$

$$\text{—CH(NHR)—N}^{-}\text{— } + \text{ M}^+ \rightarrow \text{—C(NMR)═N— } + \text{ H}_2 \qquad \text{III}$$

$$\text{—C(NMR)═N— } + \text{ H}_2\text{O} \rightarrow \text{—C(NHR)═N— } + \text{ MOH} \qquad \text{IV}$$

Where M = an alkali metal

Equation II is an equilibrium reaction and therefore both amino- and alkylamino-quinolines should be obtained depending on conditions. Although this was implied by the authors, only the most readily isolated material was reported. From the yields (Table I) experimental evidence did indicate that the 2-alkylamino base was not the only product of the reaction.

The formation of 2-methylaminoquinoline was of especial interest since in the three experiments reported, the product was isolated only with difficulty and with some doubt as to its true identity. At one point (1) it has been stated that from the reaction of quinoline, sodium-potassium amide eutectic and excess methylamine in a heated autoclave, a 26% yield of 2-methylaminoquinoline was obtained with a melting point varying between 68 and 81°. This was attributed to two "crystalline modifications." Then too, Bergstrom (2) had observed that a sample of the lower-melting 2-methylaminoquinoline could be transformed to the higher-melting modification by treatment with potassium amide in liquid ammonia.

Since an attempt was being made in this laboratory to introduce the alkylamino group directly into the 2-position of quinoline through the use of lithium alkylamides without lithium amide as an intermediate, the above facts were of some significance. Therefore, it was decided to study the equilibrium suggested by equation II to see if both 2-amino- and 2-alkylamino-quinoline could not be isolated approaching the reaction from either direction as well as to search for the higher melting modification of 2-methylaminoquinoline.

[1] This paper is taken in part from a thesis submitted by N. G. L. to Stanford University in partial fulfillment of the Ph.D. degree, 1948.

[2] Deceased, March 29, 1946.

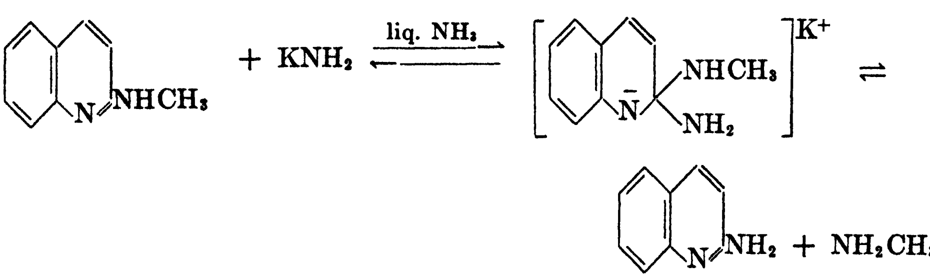
A pure sample of 2-methylaminoquinoline was prepared by treating 2-chloroquinoline with excess methylamine in a sealed tube at 100°. The product melted at 71.5° after purification. Other samples of 2-methylaminoquinoline prepared by treating quinoline-2-sulfonic acid or 2-methoxyquinoline with methylamine did not give a different melting point. 2-Methylaminoquinoline, m.p. 71.5°, was also obtained in good yield from the reaction of quinoline with lithium methylamide in anhydrous ether under nitrogen atmosphere. Extensive investigation both by this laboratory and Armour Research Foundation, Microscopy Section, of samples of 2-methylaminoquinoline obtained from various sources using the polarizing microscope and the methods of fusion analysis (3) revealed no other stable crystalline modification.

TABLE I

REACTIONS OF PYRIDINE AND QUINOLINE WITH NA-K EUTECTIC IN ALKYLAMINES (1)

BASE	AMINE	YIELD
Quinoline	Cyclohexylamine	77% 2-Cyclohexylaminoquinoline
Pyridine	"	34% 2-Cyclohexylaminopyridine
Quinoline	*n*-Butylamine	40% 2-*n*-Butylaminoquinoline
Pyridine	"	50–64% 2-*n*-Butylaminopyridine
Pyridine	*n*-Heptylamine	21% 2-*n*-Heptylaminopyridine
Pyridine	Methylamine	73% 2-Methylaminopyridine

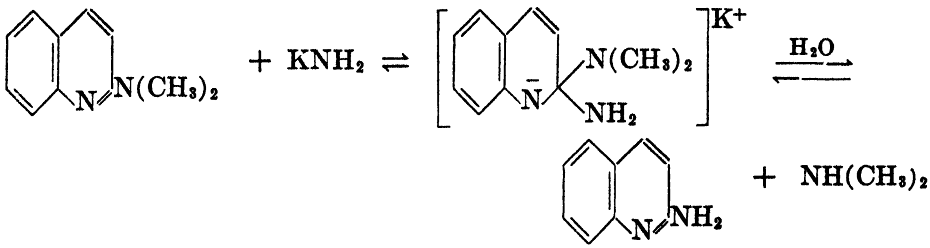
When 2-methylaminoquinoline was allowed to react with potassium amide or a mixture of sodium and potassium amide in liquid ammonia at room temperature, both 2-amino- and 2-methylamino-quinoline were isolated:



This was an approach from the right-hand side of the equilibrium in equation II. The presence of an addition compound which is implied by equation I in the forward reaction was substantiated by a brilliant yellow color when the reactants were mixed in liquid ammonia. It was shown that neither 2-methylaminoquinoline nor potassium amide alone give this characteristic color in liquid ammonia; the colored addition compound persists even when exposed to air and does not disappear until hydrolysis is complete.

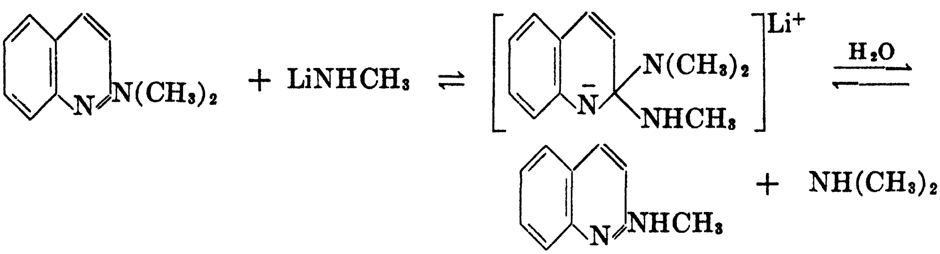
Furthermore, when 2-dimethylaminoquinoline was combined with potassium amide in liquid ammonia at room temperature for eighteen hours, 2-aminoquino-

line was readily isolated by fractional recrystallization. This was a much shorter time than that necessary for the previous experiment.



That the equilibrium favored the formation of 2-aminoquinoline was not surprising since 2-dimethylaminoquinoline could not be obtained from the reaction of quinoline with potassium dimethylamide in excess dimethylamine nor with lithium dimethylamide in ether solution and nitrogen atmosphere.

Finally when 2-dimethylaminoquinoline was allowed to react with lithium methylamide in anhydrous ether and inert atmosphere, 2-methylaminoquinoline was isolated.



The separation and isolation of the two products from any one of the reactions presented a difficult problem. While 2-aminoquinoline melted at 129–130°, 2-methyl- and 2-dimethyl-aminoquinoline both melted at approximately 70° and all three had very similar solubilities in most organic solvents. Therefore, more sensitive methods were needed for identification and separation of the two components of an equilibrium mixture. Observation of the optical properties through use of the polarizing microscope combined with the methods of chromatographic adsorption analysis (4, 5) were successfully employed.

Between the crossed nicols of a polarizing microscope it was shown that 2-amino- and 2-methylamino-quinoline have easily recognizable crystalline characteristics and form a eutectic when allowed to approach each other as they crystallize from the melt. Then too, by taking a series of melting points in capillaries using varying compositions of the two compounds, a phase diagram was obtained which indicated a eutectic at approximately 23% 2-methylaminoquinoline and 77% 2-aminoquinoline.

The anomalous melting point reported by Bergstrom and Sturz (1) for 2-methylaminoquinoline probably indicates that their product was a mixture of 2-amino- and 2-methylamino-quinoline melting at about 80°. This mixture could result as indicated in the equilibrium by the action of the excess amide ion used in the preparation.

The fact that all three compounds, 2-amino-, 2-methylamino-, and 2-dimethylamino-quinoline fluoresce in ultraviolet light made separation of any one component of the mixture (resulting from an equilibrium reaction) on a column of activated alumina an easy task. The compounds were adsorbed from a solution of petroleum ether (35–65°) and developed by washing with a 5% acetone-petroleum ether solution. They were eluted in the predicted order; 2-dimethylaminoquinoline was most readily displaced followed by 2-methylaminoquinoline, and 2-aminoquinoline could be washed down best with the addition of 1% alcohol to the acetone-petroleum ether solvent.

Thus, through quantitative separation and identification of the products of the experiments the existence of the equilibria was established.

EXPERIMENTAL

Treatment of 2-methylaminoquinoline with sodium-potassium amide in liquid ammonia. Into a long combustion-type tube contained in a Dry Ice-acetone bath was placed a small porcelain boat containing 0.2 g. of pure 2-methylaminoquinoline. An excess of a mixture of sodium and potassium amide, 1.5 g., was added and 30 ml. of ammonia distilled into the tube which was then sealed. At once an intense yellow solution formed which did not change color on standing. The contents of the tube were shaken occasionally because the slightly soluble amides tended to settle to the bottom.

After five days the tube was opened and the excess ammonia evaporated into the hood, but the yellow color (addition compound ?) persisted and did not finally disappear until hydrolysis was completed. Hydrolysis was accomplished through the cautious addition of moist benzene at first, followed by a mixture of benzene and water. The benzene layer was separated and dried over sodium hydroxide; finally it was filtered and concentrated so that only a brown oil remained. This oil was extracted four times with petroleum ether (55–85°) using 80 ml. of the solvent. Upon standing, the residue solidified to a few brown crystals, m.p. 125–129° (the melting point of 2-aminoquinoline is 129–130°).

The picrate recrystallized from alcohol, m.p. 250–253°, did not lower the melting point of the picrate of a known sample of 2-aminoquinoline. The petroleum ether extracts yielded fractions containing varying compositions of 2-methylamino- and 2-amino-quinoline melting from 58–70°.

The experiment was repeated using twelve, twenty-four, and forty-eight hours, but much lower yields were obtained than when 5–7 days were allowed in which approximately 15% yield of 2-aminoquinoline was obtained.

The various fractions were investigated between the crossed nicols of the polarizing microscope. By repeated recrystallization from the melt, the two components were concentrated, each with its own characteristic habit. Slides were made up with known mixtures of 2-amino- and 2-methylamino-quinoline and compared with the products of the equilibrium experiments whose existence could readily be recognized.

Separation by chromatographic adsorption. A 48-cm. Pyrex glass column was filled with 32 cm. of activated alumina, grade F-20, 80–200 mesh, activity 2–3 on the Brockman scale. An aliquot sample of the product from the 7-day equilibrium reaction was dissolved in 50 ml. of petroleum ether (35–65°) and poured on the activated alumina. Gentle suction was used to speed the liquid so that the drops were collected at the rate of 30–40 per minute. In a dark room when a G.E. BH-4, 100-watt mercury arc lamp was used as a source of ultraviolet illumination, it was noted that all the material was adsorbed in the first few centimeters of the column and fluoresced a beautiful violet color. Development with 5% acetone-petroleum ether solution caused separation into two bands which soon had 8–10 cm. distance between them. The material comprising the two bands was collected and separated by further development.

Evaporation of the solvent yielded white crystalline materials, and the first fraction was

identified as 2-methylaminoquinoline by its melting point, 70–71°, and by the fact that it did not lower the melting point of a known sample of the compound. The second fraction was similarly identified as 2-aminoquinoline.

Treatment of 2-dimethylaminoquinoline with sodium amide in liquid ammonia. Into a long combustion-type tube was placed a small procelain boat containing 0.026 g. of 2-dimethylaminoquinoline, m.p. 71–72°, which had previously been prepared from 2-chloroquinoline and dimethylamine in a sealed tube reaction. Another porcelain boat was used to insert 1 g. of sodium amide, and 30 ml. of ammonia were distilled in after which the cooled tube was sealed and allowed to stand at room temperature for eighteen hours. The familiar bright yellow color developed although not as bright as with 2-methylaminoquinoline.

After the tube was opened and the ammonia evaporated, the yellow-colored mass was hydrolyzed by several small additions of benzene and water. The benzene layer was separated and dried, the excess solvent removed under reduced pressure, and the remaining light brown oil solidified on standing. After three extractions using petroleum ether (35–65°), a light brown crystalline material was obtained, m.p. 125–128°. The first crystals which came out of the petroleum ether extracts were filtered, m.p. 123–125°. A mixture melting point with a known sample of 2-aminoquinoline (m.p. 129–130°) was 127–129°. The picrate of the product melted from 253–256° and did not lower the melting point of the picrate of a known sample of 2-aminoquinoline.

From the weight of 2-dimethylaminoquinoline recovered and the 2-aminoquinoline obtained, the ratio was found to be 3:1. Separation by chromatographic adsorption as in the first experiment on a column of activated alumina gave two bands, the first being identified as 2-dimethylaminoquinoline and the second 2-aminoquinoline.

Treatment of 2-dimethylaminoquinoline with lithium methylamide in ether. Phenyllithium was prepared by adding 4.5 g. (0.028 mole) bromobenzene dropwise to 200 ml. of anhydrous ether in which was suspended 0.3 g. (0.428 mole) of freshly cut, thin slices of lithium. The whole was contained in a 500-ml., 3-necked flask in the bottom of which was sealed a three-way stopcock. After the bromobenzene had been converted to phenyllithium as evidenced by warming of the flask and development of a pale purple color, the sludge of oxides and minute pieces of excess lithium was drained and then the stopcock turned so that the solution flowed by gravity into a second three-necked flask. The second round bottom flask contained an ether solution of anhydrous methylamine and as the phenyllithium flowed in, lithium methylamide was formed with some evolution of heat and formation of a creamy precipitate. An ether solution of 1.12 g. of 2-dimethylaminoquinoline was added and the mixture was refluxed for six hours, then kept at room temperature for forty hours. At all times nitrogen atmosphere was maintained throughout the system. The now familiar yellow color of the addition complex developed not unlike those in the previous experiments.

After hydrolysis using benzene and water, the ether-benzene layer was dried and finally evaporated almost to dryness. The yellow-brown oil that remained was taken up in 1:1 hydrochloric acid and extracted with ether in order to free the quinoline bases from unreacted bromobenzene and small amounts of diphenyl which might have formed in the reaction. The base was regenerated with aqueous ammonia and extracted with benzene which was dried and concentrated. Petroleum ether (35–65°) was added and the solution subjected to chromatographic adsorption analysis on activated alumina. The column was developed as before and two bands were seen to fluoresce in the presence of ultraviolet illumination. The wider band was collected and after evaporation of the solvent a white crystalline material was obtained, m.p. 69–71°, which did not lower the melting point of a known sample of 2-dimethylaminoquinoline. The second band (Fraction 2) representing a yield of approximately 2%, was a pale yellow oil which did not readily solidify. A milligram of this oil was used to form a picrate which was washed by decantation after centrifuging using a 1-ml. tube. The melting point of the picrate was approximately 226° and did not lower the melting point of the picrate of a known sample of 2-methylaminoquinoline.

The remainder of the material was dissolved in ethyl alcohol and its adsorption spectrum found using the Beckman spectrophotometer.

Fraction 2: max. 244 mu; min. 305 mu; max. 340 mu.
2-Methylaminoquinoline: max. 244 mu; min. 300 mu; max. 340 mu.
2-Dimethylaminoquinoline: max. 250 mu; min. 296 mu; max. 350 mu.

A sample of the 2-dimethylaminoquinoline used as starting material was also subjected to chromatographic adsorption to detect any impurity which might have been present. Only one fluorescent band was observed when the column was illuminated with ultraviolet light. In view of the sensitivity of the method, it was concluded that the original compound was pure and had contained no trace of 2-methylaminoquinoline previous to the experiment.

SUMMARY

1. When either 2-methylamino- or 2-dimethylamino-quinoline was treated with a mixture of sodium-potassium amide or alkali amide alone, in liquid ammonia at room temperature a bright yellow solution of an addition complex was formed which upon hydrolysis gave a mixture from which 2-aminoquinoline could be isolated. The 2-dimethylamino group was the more easily replaced by the amino group. Treatment of 2-dimethylaminoquinoline with lithium methylamide in ether solution gave a small yield of 2-methylaminoquinoline.

2. These facts substantiated the equilibrium mechanism proposed for the reaction of quinoline with alkali amides or alkylamides in liquid ammonia and perhaps other solvents in which it is proposed that there is the formation of an intermediate complex.

3. It was shown that 2-amino-, 2-methylamino-, and 2-dimethylamino-quinoline fluoresce when adsorbed on a column of activated alumina and subjected to ultraviolet light. The separation of the products of the equilibrium experiments was accomplished quantitatively by chromatographic adsorption analysis and further confirmed by melting points, mixed melting points, investigation of optical properties, and comparison of adsorption curves with the pure known compounds.

4. Using the methods of fusion analysis and the polarizing microscope, it was shown that no stable isomorphic form of 2-methylaminoquinoline having an 80° melting point exists as has previously been claimed in the literature.

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[CONTRIBUTION FROM THE VENABLE CHEMICAL LABORATORY OF THE UNIVERSITY OF NORTH CAROLINA]

THE PREPARATION OF 5-FLUORONICOTINIC ACID AND 5-FLUORONICOTINAMIDE[1]

G. F. HAWKINS AND ARTHUR ROE

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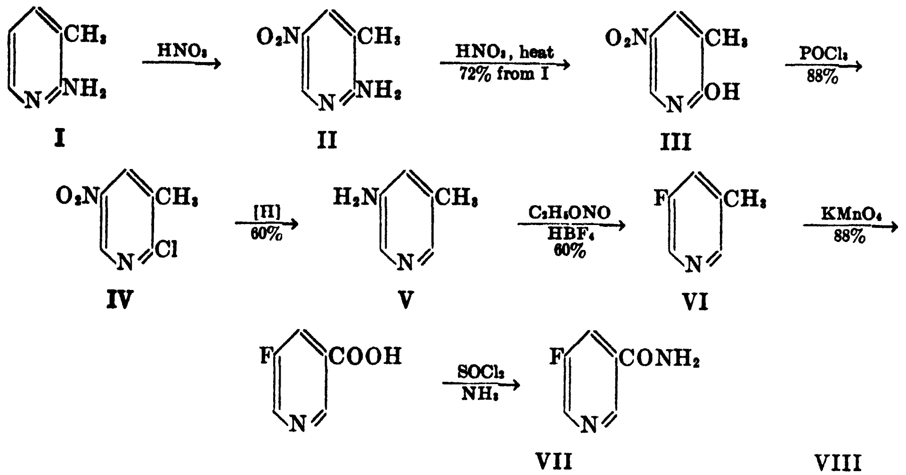
The preparation of several vitamins with fluorine replacing one or more hydrogen atoms has been undertaken as part of a study of aromatic and heterocyclic fluorine compounds being carried out in this Laboratory. Our interest in these compounds was heightened by the observation of Mitchell and Niemann (1) that 3-fluorotyrosine and 3-fluorophenylalanine act as growth inhibitors for *Neurospora crassa* 8815-3a. It was of interest to see if fluorinated vitamins would also behave as antimetabolites.

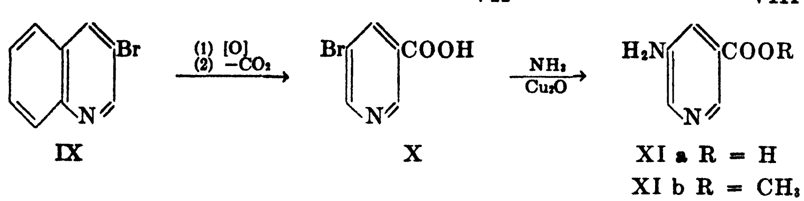
The preparation of 2- and 6-fluoronicotinic acid has already been reported (2); neither behaved as an antimetabolite. It should be noted, however, that each of these acids has a fluorine atom adjacent to the heterocyclic nitrogen; this greatly alters the basicity of that nitrogen, as shown by the fact that 2-fluoropyridine will not form a hydrochloride, whereas 3-fluoropyridine forms a stable hydrochloride. These facts indicate that 5-fluoronicotinic acid might more nearly resemble nicotinic acid in behavior than either the 2- or 6-fluoro isomer.

Two methods of synthesis of 5-fluoronicotinamide were found. The most satisfactory one started with 2-amino-3-methylpyridine, and is shown in the accompanying equations. 2-Hydroxy-3-methyl-5-nitropyridine (III) was obtained in good yield by conversion (3) of 2-amino-3-methylpyridine (I) to 2-amino-3-methyl-5-nitropyridine (II); this compound was not isolated but converted to the nitramine, which upon being heated formed 2-hydroxy-3-methyl-5-nitropyridine (III). This conversion of a nitraminopyridine to a hydroxypyridine has been observed before (4). A good yield of 2-chloro-3-methyl-5-nitropyridine (IV) was obtained by the action of phosphorus oxychloride on (III). Simultaneous reduction of the nitro group and removal of chlorine was effected by hydrogenation catalyzed by palladium-charcoal; the 3-methyl-5-aminopyridine (V) so prepared was converted to 3-methyl-5-fluoropyridine (VI) by a modification of the Schiemann reaction (5). Permanganate oxidation of (VI) produced 5-fluoronicotinic acid (VII); this was converted to 5-fluoronicotinamide using thionyl chloride and ammonia.

Several variations of the procedure outlined above were attempted. The preparation of 2-hydroxy-3-methyl-5-nitropyridine (III) by nitration of 2-hydroxy-3-methylpyridine, or by the diazotization of 2-amino-3-methyl-5-nitropyridine (II) was not very successful. Conversion of (II) to 2-chloro-3-methyl-5-nitropyridine (IV) by diazotization was accomplished in only 32% yield. Attempted deamination of 2-amino-3-methyl-5-nitropyridine (II) was completely unsuccessful; the amine would not diazotize in ethanol-sulfuric acid, and diazotization in hypophosphorus acid produced only 2-hydroxy-3-methyl-5-nitropyridine (III).

[1] The work here reported is taken from the Ph.D. Thesis of G. F. Hawkins.





A second method of preparing 5-fluoronicotinamide (VIII) starting with 3-bromoquinoline (IX) by way of 5-bromonicotinic acid (X) is outlined in the accompanying equations. Difficulty was encountered in the conversion of 5-aminonicotinic acid (XIa) to 5-fluoronicotinic acid by the Schiemann method because the diazonium fluoborate was soluble; the methyl ester (XIb) was no better in this respect. A poor yield of methyl 5-fluoronicotinate was obtained, however, using the diazonium fluosilicate (6) of (XIb); this ester was converted to 5-fluoronicotinamide (VIII). While the overall yield of this method was low, it served as a confirmation of the structure of 5-fluoronicotinic acid and its amide.

Preparation of 5-fluoronicotinic acid by oxidation of 3-fluoroquinoline (analagous to the preparation of (X) from (IX)) was attempted by several methods, all of which failed; the oxidation product contained no fluorine. Further study of this oxidation is in progress.

A study of the behavior of these compounds as antimetabolites is being made by Eli Lilly and Company, and will be reported elsewhere.

Acknowledgment: The authors are happy to acknowledge the generous support given this and related projects by Eli Lilly and Company.

EXPERIMENTAL

All melting points are corrected.

2-Hydroxy-3-methyl-5-nitropyridine (III). Method A. A solution of 50 g. of 2-amino-3-methylpyridine (I) (Reilly Tar and Chemical Corporation) in 240 ml. of conc'd sulfuric acid was cooled to 5° in an ice-salt bath. A mixture of 35 ml. each of conc'd sulfuric acid and conc'd nitric acid was added slowly with stirring, the temperature being kept below 10°. This mixture was then allowed to warm up to 30° overnight to convert (3) the nitramine to

2-amino-3-methyl-5-nitropyridine (II). (This product could be isolated at this point by pouring the mixture over cracked ice, neutralizing, and filtering off the yellow precipitate; it was found that better yields of (III) were obtained by carrying on the reaction without isolation of the intermediate.) The solution was stirred rapidly while 35 ml. of conc'd nitric acid was added at such a rate as to keep the temperature below 40°. Approximately 50 ml. of the solution was then poured into 100 ml. of water and heated to 120°; large quantities of gas were evolved. When gas evolution ceased the remainder of the nitrating mixture was added in 50-ml. portions with heating if necessary. When the last of the nitrating mixture had been added the solution was cooled rapidly by placing in an ice-bath and by adding ice directly to the solution; this is done to prevent darkening of the product, which proceeds rapidly at the temperature of the reaction. About 1 kg. of cracked ice was necessary to bring the temperature to 5°; the light brown precipitate weighing 46 g. was filtered off. An additional 5 g. of product was obtained by adding 10 g. of sodium nitrite to the filtrate, with stirring, and allowing to stand at room temperature. Still another 6 g. was obtained by neutralizing the filtrate from the sodium nitrite treatment; however a large amount of base and much time is required to recover this 6 g. The combined crude product was dissolved in the minimum quantity of dilute sodium hydroxide solution, stirred with charcoal, and filtered. The product was precipitated with dilute hydrochloric acid and filtered; the yield of 51 g. (71.5%) was pure enough for the next step. For analysis two further recrystallizations from hot water and decolorizing with charcoal produced a pale green-yellow solid, m.p. 228.5–229.5°. The compound was identical with that produced by the nitration of 2-hydroxy-3-methylpyridine (method B).

Anal. Calc'd for $C_6H_6N_2O_3$: N, 18.18. Found: N, 18.17, 18.37.

Method B. A solution of 20 g. of 2-hydroxy-3-methylpyridine [a by-product in the preparation (2) of 2-fluoro-3-methylpyridine] in 40 ml. of conc'd sulfuric acid was cooled to 10°. A mixture of 15 ml. of fuming nitric acid and 20 ml. of conc'd sulfuric acid was added slowly while keeping the temperature below 40°; when addition of the nitrating mixture was complete the solution was removed from the ice-bath and cooled as needed to keep the temperature below 50°. After 2.5 hours the solution was poured over cracked ice; considerable quantities of oxides of nitrogen were evolved, and a precipitate settled to the bottom. The precipitate was filtered, washed with water, and dried over phosphorus pentoxide overnight; the yield was 13.5 g. of cream colored III, m.p. 228.5–229.5°. A mixed melting point of this product and that prepared by method A was not depressed.

Preparation of 2-chloro-3-methyl-5-nitropyridine (IV). Method A. A mixture of 83 g. of 2-hydroxy-3-methyl-5-nitropyridine (III) and 400 ml. of phosphorus oxychloride was refluxed for 6 hours. The excess phosphorus oxychloride was then distilled off and the residue poured over cracked ice. The solid was filtered, and the filtrate neutralized with sodium hydroxide solution and extracted twice with 100-ml. portions of ether. The filtered solid was then dissolved in the ether, a small amount of heavy dark liquid settling out was discarded, and the ether layer dried overnight over calcium oxide. Distillation produced 81.5 g. (87.6%) of a pale yellow solid; m.p. 47–48°; b.p. 145.5° at 18 mm.

Anal. Calc'd for $C_6H_5ClN_2O_2$: N, 16.24. Found: N, 16.04.

Method B. Diazotization of 2-amino-3-methyl-5-nitropyridine (II). A solution of 25 g. of 2-amino-3-methyl-5-nitropyridine (II) in 200 ml. of conc'd hydrochloric acid was cooled to 20°, and 25 g. of calcium chloride was added with stirring. A saturated aqueous solution containing 13 g. of sodium nitrite was added slowly, the temperature being kept below 30°. The solution was stirred thirty minutes after the addition was complete, and allowed to stand three hours at room temperature. The product was then distilled with steam, the distillate eventually being cooled in an ice-bath to solidify the product which was filtered, washed, and dried. A yield of 9 g. (32%) was obtained, m.p. 47–48°; a mixed melting point with material prepared by method A showed no depression.

Anal. Calc'd for $C_6H_5ClN_2O_2$: N, 16.24. Found: N, 16.46.

The residue in the distilling flask was filtered hot, then cooled in an ice-bath. A precipitate of 7 g. of 2-hydroxy-3-methyl-5-nitropyridine (III) was obtained; this material was

identical in melting point with that described above, and a mixed melting point showed no depression.

Preparation of 3-methyl-5-aminopyridine (V). A solution of 24 g. of 2-chloro-3-methyl-5-nitropyridine (IV) in 100 ml. of glacial acetic was prepared; 14 g. of anhydrous sodium acetate and 5 g. of palladium-charcoal catalyst (7) were added. The mixture was shaken with hydrogen at 15 to 25 pounds pressure. At first the reaction was rapid and exothermic; after 70% of the theoretical amount of hydrogen had been adsorbed, however, it was necessary to heat the mixture with a lamp to force the reaction to continue; even with the addition of fresh catalyst, only 80% of the calculated hydrogen was taken up. The hot solution was filtered and evaporated to dryness. The residue was made strongly basic with conc'd sodium hydroxide and heated for 30 minutes. It was then cooled and extracted with three 75-ml. portions of ether; the solution was dried overnight with sodium hydroxide pellets. Distillation gave 9 g. (59.9%) of material whose melting point was 57–59°; b.p. 153°at 21 mm.

Anal. Calc'd for $C_6H_8N_2$: N, 25.91. Found: N, 26.09.

Preparation of 3-methyl-5-fluoropyridine (VI). A solution of 12 g. of 3-methyl-5-aminopyridine (V) in a mixture of 50 ml. of 42% fluoboric acid and 75 ml. of ethanol was cooled to −10°. Ethyl nitrite was passed in with stirring; the solution was kept below −5°. Precipitation suddenly occurred after about twenty minutes; ethyl nitrite was passed in until there was no more precipitation. The solution was poured into a mixture of 75 ml. of absolute alcohol and 100 ml. of ethyl ether which was cooled to −70° with Dry Ice; the solution was filtered and the white precipitate washed twice with cold absolute ethanol, twice with cold dry ether, and twice with petroleum ether (b.p. 30–60°) previously dried over phosphorus pentoxide. (Caution: do not allow the solid to dry; it is unstable if all solvent is removed.) The solid, dampened with petroleum ether, was transferred to a 500-ml. round-bottom flask containing 75 ml. of dried petroleum ether; a condenser was fitted to the flask. The mixture was gently warmed to initiate decomposition of the diazonium salt; the mixture was then cooled as necessary to prevent too vigorous a reaction. When the reaction seemed complete the mixture was refluxed for 30 minutes, and the solvent decanted. The petroleum ether was extracted twice with 50 ml. of dilute hydrochloric acid; these extracts were added to the flask and warmed to remove all the petroleum ether. The contents of the flask were made slightly alkaline and distilled; the 3-methyl-5-fluoropyridine was quite volatile with steam. The distillate was saturated with sodium sulfate and a few drops of sodium hydroxide were added. The organic liquid was separated, dried over sodium hydroxide pellets, and distilled. The yield of colorless 3-methyl-5-fluoropyridine was 7.4 g. (60%); b.p. 139° at 760 mm.; d^{25} 1.0837; n_D^{25} 1.4788.

Anal. Calc'd for C_6H_6FN: N, 12.61. Found: N, 12.68.

Preparation of 5-fluoronicotinic acid (VII). A mixture of 8.5 g. of 5-fluoro-3-methylpyridine and 600 ml. of water was placed in a liter flask fitted with a reflux condenser. Potassium permanganate was added to the refluxing solution, 8 g. at first, and then little by little as the solution decolorized until 26 g. had been added; the process required about three hours. The unreacted 3-methyl-5-fluoropyridine (2.8 g.) was removed by distillation, the residue in the flask filtered while hot, and the precipitate washed with hot water which was added to the filtrate. The colorless solution was evaporated to a volume of 150 ml., when hydrochloric acid was added slowly until precipitation was complete. The solid was filtered and the filtrate evaporated to 50 ml., more hydrochloric acid added, whereupon more solid precipitated. The precipitate (6.4 g., 88.4% based on amount of 3-methyl-5-fluoropyridine consumed) was recrystallized from water, yielding 5.7 g. (77.3%) of 5-fluoronicotinic acid, m.p. 195–197°.

Anal. Calc'd for $C_6H_4FNO_2$: N, 9.93. Found: N, 10.03, 10.10.

Preparation of 5-fluoronicotinamide (VIII). A solution of 3 g. of 5-fluoronicotinic acid in 50 ml. of thionyl chloride was refluxed for 12 hours; at the end of that time the excess thionyl chloride was removed by distillation at reduced pressure. Distillation of the product gave 1.5 ml. of material, b.p. 82° at 18 mm. Anhydrous ammonia was allowed to react with this acid chloride; the crude amide was twice recrystallized from water, yielding 1.1 g. of 5-fluoronicotinamide, m.p. 173–175°.

Anal. Calc'd for $C_6H_5FN_2O$: N, 20.00. Found: N, 20.03.

Preparation of methyl 5-aminonicotinate from 3-bromquinoline. The method of Graf (8) was used to convert 45 g. of 3-bromoquinoline (IX) (obtained from Eastman) to 16.5 g. of 5-bromonicotinic acid (X). Following the method of Meyer and Graf (9) 14.5 g. of 5-bromonicotinic acid was converted to 6.5 g. of 5-aminonicotinic acid (XIa). Reaction of this acid with diazomethane produced 3 g. of methyl 5-aminonicotinate (XIb), m.p. 135–137° [lit. value (9) 137°].

Preparation of 5-fluoronicotinamide (VIII). Attempts to prepare this compound from the amino acid (XIa) or its methyl ester (XIb) by the modified Schiemann reaction (5) were not successful because of the solubility of the diazonium fluoborate in both cases. Preparation was possible using the diazonium fluosilicate, however (6). A solution of 2.7 g. of methyl 5-aminonicotinate (XIb) in 50 ml. of 95% ethanol was treated with 25 ml. of 30% fluosilicic acid. The precipitated salt was filtered off and suspended in 50 ml. of glacial acetic acid; ethyl nitrite was passed into the solution until the solid had dissolved, the temperature being kept below 32° during the process. The solution was cooled in an ice-bath, and 75 ml. of dry ether was added to precipitate the diazonium fluosilicate, which was filtered and washed once with absolute ethanol and thrice with dry ether. This process was carried out in an atmosphere of carbon dioxide to prevent absorption of water by the diazonium salt. The salt weighed 4.5 g. after drying overnight in a desiccator over phosphorus pentoxide; m.p. 89° with violent decomposition. The salt was suspended in dry toluene and heated until decomposition was complete. The toluene layer was then dried over sodium sulfate and distilled; 0.4 g. of methyl 5-fluoronicotinate was obtained; b.p. 101–102° at 26 mm.; m.p. 46–50°.

Anal. Calc'd for $C_7H_6FNO_2$: N, 9.03. Found: N, 9.47.

This apparently impure ester was dissolved in 50% methanol, the solution cooled in an ice-bath, and saturated with ammonia. After standing 16 hours, the solution was evaporated to a small volume and filtered; the 5-fluoronicotinamide so formed after one recrystallization from water melted at 173–175°, and did not depress the melting point of a sample of the material prepared from 2-amino-3-methylpyridine described above.

Oxidation of 3-fluoroquinoline. A mixture of 5 g. of 3-fluoroquinoline (10) and 50 ml. of water was heated to boiling, and 32.5 g. of $KMnO_4$ dissolved in water was added through a dropping-funnel over a period of an hour. The reaction mixture was worked up exactly as described for 5-fluoronicotinic acid above. Acidification caused precipitation of a white material which did not contain fluorine. Further investigation of this product is under way. Oxidation by the method of Graf (8) and oxidation with conc'd nitric acid also failed to produce any 5-fluoronicotinic acid.

SUMMARY

Two methods of synthesis of 5-fluoronicotinamide are reported, as well as attempts to prepare it by a third method. Seven new compounds were prepared in the course of the investigation.

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[Contribution from the Chemistry Department of the University of Missouri]

THE ISOMERIC 4-*n*-PROPYLCYCLOHEXANOLS

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Received December 6, 1948

In a previous communication from this laboratory (1) it was shown that mixtures of isomers resulting from the reduction of 4-*n*-propylcyclohexanone with platinum in acetic acid gave viscosities much smaller (η^{25} 0.098–0.125 than either of the pure isomers (η^{25} 0.313 and 0.688) or a mixture of approximately equal amounts of the isomers (η^{25} 0.456). Since the molecular refractions of the low-viscosity mixtures agreed closely with the calculated value, it was tentatively suggested that the mixtures might contain a third stable isomer. Further investigations of solid 4-substituted cyclohexanols have shown that *cis* and *trans* forms of such compounds exist in only one form and no other isomers are present since all mixtures can be explained on the basis of the melting point-composition diagrams of the pure isomers (2). A subsequent reinvestigation of the low-viscosity mixtures of the 4-*n*-propylcyclohexanols has established the presence of a small amount of 4-*n*-propylcyclohexanone.

The ketone was separated by fractional distillation of the mixture (66.0 g.) through a 30-plate Fenske column under reduced pressure with a reflux ratio of approximately 50:1. It boiled at 97–98° (20 mm.), yield 5.3 g., and had d_{25}^{25} 0.9002, n_D^{25} 1.4530, η^{25} 0.0278. The semicarbazone melted at 181–182° and did not depress the melting point of an authentic specimen. The low viscosity of the contaminating ketone (η^{25} 0.0227 for purified 4-*n*-propylcyclohexanone) explains the abnormal values obtained for the viscosities of the mixtures.

Unchanged ketone remains in mixtures of isomeric alkylcyclohexanols obtained by catalytic hydrogenation over platinum catalyst even though the theoretical amount of hydrogen is taken up because of the accompanying hydrogenolysis of the hydroxyl group.

Similar abnormally low viscosities (η^{25} 1.55) have been observed by v. Auwers and Dersch some time ago for the cyclohexanol mixture obtained by reduction by 2-methylcyclohexanone with platinum in acetic acid (3). Derivatives of the *trans* alcohol could be isolated from mixtures with viscosities corresponding to that of the pure *cis* isomer (η^{25} 1.71). The postulated inversion of the *cis* alcohol suggested by the authors as a possible explanation for these results has been disproven independently by Skita and Faust (4) and by Hückel and Hagenguth (5). It is now reasonable to assume that v. Auwers' mixtures contained 2-methylcyclohexanone (η^{20} 0.0176) (6).

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[CONTRIBUTION FROM THE LABORATORY OF CHEMISTRY AND CHEMOTHERAPY, EXPERIMENTAL BIOLOGY AND MEDICINE INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

FUNCTIONAL DERIVATIVES OF THE ANTIMALARIAL 9-(2-DIAMYLAMINO-1-HYDROXYETHYL)-1,2,3,4-TETRAHYDROPHENANTHRENE (SN 1796[1])

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Received December 13, 1948

Within the malaria research program carried out by the Section on Chemotherapy of this Laboratory it became advisable to synthesize two derivatives of the very active antimalarial 9-(2-diamylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene (SN 1796) (1). The first compound, 9-(1-chloro-2-diamylaminoethyl)-1,2,3,4-tetrahydrophenanthrene (SN 8845), is distinguished from SN 1796 by having the hydroxyl group replaced by chlorine; it was prepared from the parent compound by the action of phosphorus pentachloride. The second compound, 9-(2-diamylaminoethyl)-1,2,3,4-tetrahydrophenanthrene (SN 11,580), is the desoxy derivative of SN 1796; it was prepared from the chloro compound by hydrogenation in the presence of a palladium catalyst.

While the chloro compound showed about the same antimalarial activity as SN 1796 (Q 0.3, *Plasmodium gallinaceum*), the desoxy compound was inactive. Neither compound showed any activity on sporozoite-induced *gallinaceum* malaria (2).

$C_{14}H_{13}$-9-$CHOHCH_2N(C_5H_{11})_2$	SN 1796
$C_{14}H_{13}$-9-$CHClCH_2N(C_5H_{11})_2$	SN 8845
$C_{14}H_{13}$-9-$CH_2CH_2N(C_5H_{11})_2$	SN 11,580

EXPERIMENTAL PART

9-(1-Chloro-2-diamylaminoethyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride (SN 8845). Although consistently high yields of this compound were not obtained, the most satisfactory procedure was as follows. To 8.4 g. of powdered phosphorous pentachloride suspended in 100 ml. of alcohol-free, dry chloroform was added gradually 8.4 g. of 9-(2-diamylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride (1). The flask containing the mixture was shaken gently in a bath of cold water until homogeneous, then left overnight at room temperature. If ether was added at this point, an oil precipitated and became crystalline spontaneously in the course of several hours. This material appeared to be an addition compound of the desired chloride with a phosphorus halide and was not investigated further. Instead, the original chloroform solution was concentrated *in vacuo* and the resulting oil was shaken for a few minutes with 100 ml. of absolute ether to extract as much of the phosphorus halides as possible. The mixture was left in the refrigerator overnight or longer until the oil had crystallized completely. The ethereal solution was then decanted, and the solid residue was decomposed carefully by shaking it with ice and ether to which small amounts of sodium carbonate were added from time to time until the aqueous layer remained slightly alkaline. The ethereal layer containing the free organic

[1] The Survey Numbers, designated SN, correspond to those listed in F. Y. Wiselogle, "A Survey of Antimalarial Drugs, 1941–1945," J. W. Edwards, Ann Arbor, 1946.

base was separated, washed with water, dried with Drierite, and concentrated *in vacuo* to a sirup. An equivalent amount of methyl alcoholic hydrogen chloride was added, and the mixture was concentrated *in vacuo* to a sirup which could be crystallized with ether and isopentane. The yield was 8.0 g. For analysis the substance was recrystallized thrice from a small amount of methyl alcohol by the addition of ether and isopentane. The product, bundles of thin plates, sintered at about 82° and melted at 89–91° to a yellowish melt; after standing for several weeks in a desiccator, the crystals melted at about 95°; they became brownish yellow on continued exposure to light.

Anal.[2] Calc'd for $C_{26}H_{39}ClN \cdot HCl$: C, 71.54; H, 9.01; Cl, 16.25; N, 3.21.
Found: C, 71.09; H, 8.78; Cl, 16.40; N, 2.84.

9-(2-Diamylaminoethyl)-1,2,3,4-tetrahydrophenanthrene picrate. Removal of chlorine from the preceding compound was effected by catalytic hydrogenation in the presence of palladium hydroxide (with zinc and copper hydroxides) on calcium carbonate, prepared by the method of Kuhn and Ströbele (3). A mixture of 0.3 g. of catalyst, 2.7 g. of calcium carbonate, and 75 ml. of methyl alcohol was shaken with hydrogen to reduce the catalyst, then 2.2 g. of the chloro compound was added, and the mixture was shaken with hydrogen until no further change in volume occurred. The reaction was completed within forty-five minutes at 30°, with 95 ml. of hydrogen being absorbed; the theory for complete unimolecular reduction was 124 ml. The methyl alcohol solution was filtered, concentrated *in vacuo*, and the residue extracted with ether; a small amount of aqueous sodium hydroxide was added to ensure complete liberation of the organic base. The ethereal solution was washed with water, dried with Drierite, concentrated, and the residue subjected to evaporative distillation. A mobile, yellowish oil weighing 1.5 g. was obtained between 100° and 150° at 0.1 mm. It was dissolved in ether and mixed with 1.5 g. of picric acid in absolute ethyl alcohol. Upon concentration of this solution, 1.5 g. of crystalline picrate separated; recrystallized thrice from absolute alcohol, it formed clusters of large, elongated, yellow prisms melting at 110–111°.

Anal.[2] Calc'd for $C_{32}H_{42}N_4O_7$: C, 64.62; H, 7.12; N, 9.42.
Found: C, 64.67; H, 7.09; N, 9.41.

9-(2-Diamylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene picrate. For comparison with the picrate just described, the picrate of the 2-diamylamino-1-hydroxyethyl derivative also was prepared. Four recrystallizations from absolute ethyl alcohol yielded clusters of yellow, elongated, somewhat flattened prisms which sintered at about 142°, and melted at 150–151°.

Anal.[2] Calc'd for $C_{32}H_{42}N_4O_8$: C, 62.93; H, 6.93; N, 9.17.
Found: C, 62.92; H, 7.01; N, 9.20.

9-(2-Diamylaminoethyl)-1,2,3,4-tetrahydrophenanthrene acid sulfate (SN 11,580). Preliminary experiments showed that the 2-diamylaminoethyl compound could be characterized also by the crystalline products which it formed with perchloric, *l*-malic, and sulfuric acids. For biological tests the sulfate was chosen. Accordingly, 11.4 g. of the purified picrate was dissolved in 1 liter of ether, and the solution was extracted with 10% aqueous sodium hydroxide until all the picric acid had been removed. The ethereal solution was washed with water, dried with Drierite, and concentrated to 200 ml.; an equivalent amount of concentrated sulfuric acid (1.1 ml.) was added, and the ether removed *in vacuo*. The residual sirup solidified, and was recrystallized four times from absolute ethyl alcohol by the addition of ether and isopentane. The product separated in clusters of small, thin plates which melted at 124–127° after preliminary sintering at 120°. The yield was practically quantitative. The sulfate appeared to hydrolyze to oily drops when added to water.

Anal.[2] Calc'd for $C_{26}H_{39}N \cdot H_2SO_4$: C, 67.35; H, 8.91; N, 3.02.
Found: C, 67.41; H, 8.86; N, 2.97.

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[2] The microanalyses were carried out by Dr. Arthur T. Ness of this Laboratory.

SUMMARY

The antimalarial 9-(2-diamylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene (SN 1796) has been converted to a chloro derivative (SN 8845) and a desoxy derivative (SN 11,580). The therapeutic evaluation of these derivatives is given.

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[CONTRIBUTION FROM THE INSTITUTE OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF SZEGED]

USE OF ACYL MIGRATION IN SEPARATING DIASTEREOISOMERIC AMINO ALCOHOLS

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In a recent communication (1) we reported that under the same experimental conditions *dl*-1-(3,4-diethoxyphenyl)-2-acetamido-1-propanol (IIf), synthesized from 1-(3,4-diethoxyphenyl)-1-nitroso-2-nitropropane (If), reacted instantly with hydrogen chloride in absolute alcohol to form the salt of the corresponding O-acetylamino alcohol (IIIf), whereas the N-acetyl derivative of the diastereoisomeric aminopropanol, obtained by reduction of 3,4-diethoxy-α-isonitrosopropiophenone (VIf), remained unchanged. Welsh (2) had previously observed a difference between the rates of the acetyl migration reaction of N-acetyl-*dl*-ephedrine and N-acetyl-*d*-ψ-ephedrine.

This paper deals with a comparative study on acyl migration in three different diastereoisomeric pairs of amino alcohols.

dl-Norephedrine (VIIj) was prepared from α-oximinopropiophenone (VIj) (3). *dl*-Nor-ψ-ephedrine was synthesized from propenylbenzene *via* 1-phenyl-1-nitroso-2-nitropropane and 1-phenyl-2-nitro-1-acetoxypropane, according to the principle of Bruckner's synthesis (4); the formation of norephedrine could not be detected. The *N*-benzoyl derivatives of these diastereoisomers behave differently towards alcoholic hydrogen chloride; N-benzoyl-*dl*-norephedrine did not undergo acyl migration in the course of three days at room temperature, whereas N-benzoyl-*dl*-nor-ψ-ephedrine yielded the calculated amount of O-benzoyl-*dl*-nor-ψ-ephedrine hydrochloride (5). This behavior prompted us to attempt the separation of these diastereoisomers by the acyl migration reaction. For this purpose *dl*-norephedrine was converted into a mixture of the two diastereoisomers, benzoylated and treated subsequently with hydrogen chloride in absolute alcohol. The salt of O-benzoyl-*dl*-nor-ψ-ephedrine which was formed could be separated easily from the unchanged N-benzoyl-*dl*-norephedrine through its far greater solubility in water; it was then converted by reverse acyl migration into N-benzoyl-*dl*-nor-ψ-ephedrine. The separated N-benzoylated diastereoisomers gave rise on acetylation to different O-acetyl-N-benzoyl derivatives. Their formation without inversion is at variance with the assumption of Kanao (6), *i.e.*, that esterification in the ephedrine series must always be combined with a Walden inversion. Our results are in agreement with those of Welsh (2) and of Bretschneider (7) who have conducted esterification with retention of configuration in the acetylation of ephedrine hydrochloride.

This new method for separation is all the more interesting in view of the results of Hoover and Hass (8), who were unable to separate satisfactorily *dl*-norephedrine from *dl*-nor-ψ-ephedrine.

We wanted to extend this method to the separation of acylated ephedrines

from acylated ψ-ephedrines. For this purpose N-benzoyl-*dl*-ψ-ephedrine and the corresponding derivative of *dl*-ephedrine were prepared. In alcoholic hydrogen chloride, the former showed a spontaneous benzoyl shift yielding O-benzoyl-*dl*-ψ-ephedrine hydrochloride. N-benzoyl-*dl*-ephedrine gave on similar treatment varying amounts of O-benzoyl-*dl*-ψ-ephedrine hydrochloride, depending upon the time it was kept in alcoholic hydrogen chloride. For example, on adding this reagent to N-benzoyl-*dl*-ephedrine, evaporating the solvent after a few minutes, and allowing the residue to crystallize, the main bulk of the amide was recovered; a smaller part, however, was converted into O-benzoyl-ψ-ephedrine hydrochloride because of an inversion prior to acyl migration.[1] However, the presence of an appreciable amount of inverted material was not evidenced on inoculation of the residue immediately after evaporation of the solvent.

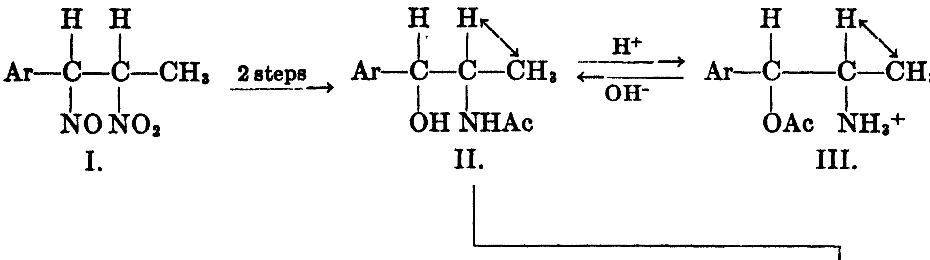
Several attempts were undertaken to separate a mixture of N-benzoylephedrine from N-benzoyl-ψ-ephedrine by treating the mixture with an excess of alcoholic hydrogen chloride for a few minutes, cautiously removing the solvent, and allowing the residual sirup to crystallize; on keeping the sirupy mixture for several days in a desiccator, only O-benzoyl-*dl*-ψ-ephedrine hydrochloride could be isolated because of an inversion of N-benzoylephedrine. However, if the mixture was extracted with water immediately after removal of alcohol, the unchanged crystalline ephedrine derivative was obtained, whereas the O-benzoyl-ψ-ephedrine salt went into solution. In this case inversion of the acylated ephedrine derivative took place to only a small extent. A still more successful separation of the diastereoisomers was achieved by adding only the amount of alcoholic hydrogen chloride equivalent to the quantity of ψ-ephedrine derivative present. This procedure should be useful in the separation of mixtures of optically active derivatives in which the content of ψ-ephedrine derivative can be calculated from rotation data.

Finally, the behavior of a diastereoisomeric pair containing a phenyl group instead of the methyl group of norephedrine was investigated. *dl*-1,2-Diphenyl-2-aminoethanol (Type VII), prepared by reduction of benzoin oxime (10), was isomerized to a mixture of the two diastereoisomers, then acetylated and treated with alcoholic hydrogen chloride. As expected, *dl*-1,2-diphenyl-2-acetamidoethanol (11a) was recovered besides *dl*-1,2-*iso*-diphenyl-2-amino-1-acetoxyethane hydrochloride (Type III) (11b). The different solubilities of the amide and the salt rendered separation easy. The hydrochloride was then converted into the neutral *dl*-1,2-*iso*-diphenyl-2-acetamidoethanol (11b), formulated erroneously as an O-acetyl base (12). The same results were obtained in the separation of mixtures of known composition which were prepared from the pure diasteroisomeric acetyl derivatives.

These examples illustrate the possibilities given by the new method of separation. Attempts to extend and to refine it are in progress.

[1] Similar changes of configuration combined with an N → O acyl shift have been recorded in the cases of other N-acylephedrines; e.g., N-*p*-nitrobenzoyl-*l*-ephedrine by the action of cold aqueous hydrochloric acid gave O-*p*-nitrobenzoyl-*d*-ψ-ephedrine hydrochloride (9). On the other hand, N-acetyl-*dl*-ephedrine yielded, under other experimental conditions, the salt of O-acetyl-*dl*-ephedrine (2).

The reason for the great difference between N-acylated norephedrine and nor-ψ-ephedrine derivatives from the point of view of acyl migration must be sought in the configurations of the two series of compounds. Similar differences are



Substituents of Ar

4-methoxy (a) (19a)

3,4-dimethoxy (b) (4)

3-methoxy-4-acetoxy (c) (19a)

3-methoxy-4-benzyloxy (d) (19c)

3,4-dibenzyloxy (e) (19b)

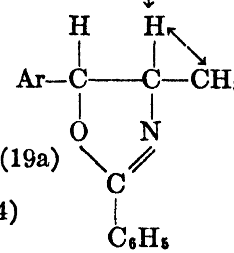
3,4-diethoxy (f) (1)

3,4-dihydroxy (g) (19b)

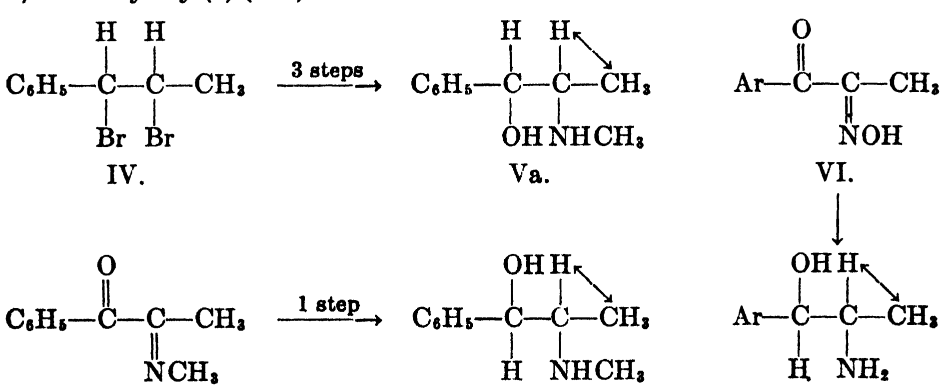
3-methoxy-4-hydroxy (h) (19a)

3,4-methylenedioxy (i) (4)

Ar = phenyl (j) (3)



IX f, j.



Substituents of Ar

3,4-dimethoxy (b) (20a)
3,4-diethoxy (f) (1)
3,4-dihydroxy (g) (20b)
3-methoxy-4-hydroxy (h) (20c)
Ar = phenyl (j)

observed in their behavior in forming an oxazoline ring. N-benzoyl-*dl*-nor-ψ-ephedrine gives by the action of cold thionyl chloride (5) the corresponding oxazoline derivative (IXj) with retention of configuration, whereas similar treatment of the appropriate norephedrine derivative results in a Walden inversion prior to condensation, and yields an oxazoline derivative related to ψ-ephedrine. In our experiments, N-benzoyl-3,4-diethoxy-*dl*-nor-ψ-ephedrine readily furnished an

oxazoline (IXf) salt as a result of the action of thionyl chloride. From the analogous diastereoisomer we were, however, unable to isolate any crystalline product. These facts may be perhaps explained by supposing that a case of restricted rotation (13, 14) occurs, in which the acylamino and hydroxyl groups are more frequently *cis* in acyl (nor)-ψ-ephedrines and *trans* in acyl (nor) ephedrines. The hydroxyl group of N-benzoylephedrine may assume a position of proximity to the acylamino group (which position is needed for acyl migration) more easily by inversion than by rotation.

Regarding ephedrine and ψ-ephedrine, Späth (15) speculated that in the molecule of ψ-ephedrine the hydroxyl and methylamino groups are placed spatially nearer to each other than in the molecule of ephedrine. Possible evidence for this supposition is presented by the fact that ψ-ephedrine, unlike ephedrine, does not form a hydrate. This difference in behavior was explained by Emde (16) as due to interaction of residual affinities of the functional groups in the ψ-isomer. The presence of a hydrogen bridge (17) between the propanol oxygen and the neighboring nitrogen of the methylamino group seems to us a better explanation; this suggestion must, however, be supported by infra red data. It is also of interest to consider that syntheses of aminopropanols (Ia-i; j; Va) starting with propenylbenzene derivatives always lead to ψ-(nor)ephedrines (18, 19). A *cis* addition of nitroso and nitro groups (or of bromine IV) to the propene double bond is more favored than a *trans* addition; if these groups are exchanged by amino and hydroxyl groups (assuming no Walden inversion takes place) the latter ought to retain the same relative positions. On the other hand, reduction of oximino or alkimino ketones (VIII) leads exclusively to (nor)-ephedrine derivatives VII or Vb (20, 21). Manske and Johnson (21) assumed that in alkimino ketones the nitrogen and oxygen atoms are spatially on opposite sides of the carbon chain, because of a repulsive effect, and that they respectively predestine the positions of the succeeding alkamino and hydroxyl groups.

All mentioned facts seem to support the validity of Späth's suggestion for ephedrine and ψ-ephedrine. However, the ready formation of different oxazolidines from ephedrine (22) and from ψ-ephedrine (23) is at variance with the behavior of acylated (nor)ephedrine derivatives. We must, however, take into consideration that restricted rotation does not exclude the possibility for rotation; it signifies only that certain steric positions are energetically more stable, and that the shift into another position requires an amount of energy (14).

The elucidation of the relative steric position of the hydroxyl and of the substtuted amino groups does not give any evidence regarding the relative steric position of H and of CH_3 in the molecule of ephedrine and ψ-ephedrine, respectively (24). We suggest new projection formulas which are more in agreement with the results of acyl migration experiments. The positions of the hydrogen atom and the methyl group on carbon atom number 2, however, still remain to be settled (25, 26).

EXPERIMENTAL

A. *dl-Norephedrine and -nor-ψ-ephedrine derivatives. O-acetyl-dl-nor-ψ-ephedrine hydrochloride from propenylbenzene.* To a mixture consisting of 30 g. (0.254 mole) of propenyl-

benzene in 150 cc. of ether and 80 g. of sodium nitrite in 100 cc. of water, 150 cc. of 20 per cent by volume sulfuric acid was added drop by drop in the course of an hour. The crystalline 1-phenyl-1-nitroso-2-nitropropane was isolated in the usual manner (4) and could be recrystallized from chloroform; yield, 40%; m.p. 129–130°.

Anal. Calc'd for $C_9H_{10}N_2O_3$: C, 55.7; H, 5.2. Found: C, 55.8; H, 5.3.

1-Phenyl-1-acetoxy-2-nitropropane. From 30 g. of the nitroso-nitro compound was obtained 26 g. of the oily nitro ester suitable for electrolytic reduction.

O-acetyl-dl-nor-ψ-ephedrine hydrochloride. An amorphous N-acetyl derivative was prepared from 11.2 g. of the nitro ester by the method of reduction described elsewhere (4). The product was converted by the action of absolute ethereal hydrogen chloride into colorless needles of the amino ester hydrochloride; m.p. 183° after recrystallization from ethyl acetate.

Anal. Calc'd for $C_{11}H_{17}ClNO_2$: C, 57.5; H, 7.0. Found: C, 57.5; H, 7.0.

dl-Norephedrine. This substance was prepared according to Hartung and Munch (3) from propiophenone via α-oximinopropiophenone. Reduction to norephedrine was carried out in two steps, as described by Hartung, *et al.* (20b) for other aryl propanolamines; yield, 91%.

N-Benzoyl-dl-norephedrine. This hydroxy amide was prepared under Schotten-Baumann conditions (5); m.p. 143°. To a solution of 0.2 g. of compound in 12 cc. of anhydrous ethanol was added 0.23 cc. of 5 *N* alcoholic hydrochloric acid. The mixture was allowed to stand for five days at room temperature in a desiccator during which time the solvent slowly evaporated. The dry residue was then dissolved in 100 cc. of hot water, the solution was cooled, the crystals separated, and the liquid concentrated; a total of 0.189 g. (94.5%) of crystals was obtained; m.p. 142–144°, alone and mixed with N-benzoylnorephedrine. The mother liquid yielded 8 mg. of crystals. Consequently, no appreciable acyl migration occurred under these experimental conditions.

Conversion of dl-norephedrine into dl-nor-ψ-ephedrine. A solution of 2 g. (0.0107 mole) of *dl*-norephedrine hydrochloride in 50 cc. of hydrochloric acid (14 g. HCl per 100 cc. water) was refluxed for twelve hours. The solvent was removed and the residue was dissolved in absolute alcohol; evaporation afforded 1.96 g. of colorless crystals, consisting of a mixture of the hydrochlorides of the two diastereoisomers; m.p. 100–135°.

Separation of dl-norephedrine from dl-nor-ψ-ephedrine. (*a*). The mixture obtained above (1.95 g., 0.0104 mole) was dissolved in 40 cc. of water, and 6 cc. of 5 *N* sodium hydroxide and 1.75 g. (0.0128 mole) of benzoyl chloride in 2 cc. of benzene were added at 40°; 2.4768 g. of a mixture of the diastereoisomeric N-benzoyl derivatives, m.p. 85–110°, was thus obtained. This was dissolved in 25 cc. of anhydrous ethanol, 3.2 cc. of 4.4 *N* hydrogen chloride (0.0141 mole) in anhydrous alcohol was added and the solution was kept for three days at room temperature. Evaporation of the alcohol *in vacuo* gave a crystalline residue, which was extracted twice with a total of 300 cc. of water. The undissolved part weighed 0.18 g., m.p. 132–136°, and was identical with N-benzoylnorephedrine (5). Concentration of the aqueous solution to 100 cc. furnished a further crop, 0.807 g. of crystals, m.p. 136–140°, identical with N-benzoylnorephedrine. Yield, 0.987 g. (40%, based upon the mixture of benzoyl derivatives). Recrystallization from benzene afforded colorless plates, m.p. 143° (5).

Anal. Calc'd for $C_{16}H_{17}NO_2$: C, 75.3; H, 6.7. Found: C, 75.3; H, 6.2.

The mother liquor was evaporated to dryness. The residue (1.213 g., 43%, based upon the mixture of benzoyl derivatives) melted at 205–210°, and was identical with O-benzoyl-*dl*-nor-ψ-ephedrine hydrochloride (5). Recrystallization of a sample from ethyl acetate gave colorless needles, m.p. 220°.

Anal. Calc'd for $C_{16}H_{18}ClNO_2$: C, 65.8; H, 6.2. Found: C, 65.5; H, 6.2.

It was further identified by reverse acyl migration (O → N), which yielded 1 g. N-benzoyl-*dl*-nor-ψ-ephedrine, m.p. 128°; recrystallized from benzene, m.p. 128°, alone and in admixture with an authentic specimen. Mixed m.p. with N-benzoyl-*dl*-norephedrine 85–110°.

Anal. Calc'd for $C_{16}H_{17}NO_2$: C, 75.3; H, 6.71. Found: C, 75.45; H, 6.7.

(*b*). *n*-Benzoyl-*dl*-norephedrine (0.20 g., 0.00082 mole) and 0.20 g. of N-benzoyl-*dl*-nor-ψ-ephedrine were dissolved in 30 cc. of anhydrous alcohol, 0.47 cc. (3 moles per 2 moles amide) of 5 *N* hydrochloric acid in anhydrous alcohol was added. The solution was kept for three days at room temperature, and finally evaporated *in vacuo*. The dried product was treated with 150 cc. of hot water, and the separated crystals were filtered off. The mother liquor gave on concentrating to 20–30 cc. a further crop of crystals. The total yield was 0.1633 g. (81.6%) of pure N-benzoyl-*dl*-norephedrine, m.p. 140–144°. The filtrate was evaporated to dryness. The residual crystals (0.20 g., 82%) showed m.p. 215–216°, alone and in admixture with O-benzoyl-*dl*-ψ-ephedrine hydrochloride.

O-Acetyl-N-benzoyl-dl-norephedrine. One-half gram (0.0049 mole) of acetic anhydride was added to a solution of 0.2 g. (0.00082 mole) of N-benzoyl-*dl*-norephedrine (obtained in the above separation) in 4 cc. of anhydrous pyridine, and the whole was allowed to stand overnight at room temperature. The solvent was then evaporated *in vacuo*, and the residual gum recrystallized from 1.5 cc. of benzene: yield, 0.11 g., m.p. 143–144°; mixed m.p. with the starting material 110–115°.

Anal. Calc'd for $C_{18}H_{19}NO_3$: C, 72.7; H, 6.4. Found: C, 72.7; H, 6.4.

O-acetyl-N-benzoyl-dl-nor-ψ-ephedrine. The crude ester was obtained from 0.4 g. (0.00164 mole) of N-benzoyl-*dl*-nor-ψ-ephedrine (obtained from the mixture of diastereoisomers) and 1 cc. (0.0098 mole) of acetic anhydride in 4 cc. of pyridine. Recrystallization from a mixture of 2 cc. of benzene and 10 cc. of petroleum ether afforded colorless plates, 0.337 g. (73%), m.p. 130–131°. On admixture with O-acetyl-N-benzoyl-*dl*-norephedrine, m.p. 104–120°; mixed with N-benzoyl-*dl*-nor-ψ-ephedrine, m.p. 99–120°.

Anal. Calc'd for $C_{18}H_{19}NO_3$: C, 72.7; H, 6.4. Found: C, 73.1; H, 6.45.

B. *dl-Ephedrine and -ψ-ephedrine derivatives. N-Benzoyl-dl-ψ-ephedrine.* This substance was obtained by using the Schotten-Baumann procedure given for the diastereoisomeric form. From 2.47 g. (0.015 mole) of ψ-ephedrine, 3.65 g. (90.3%) of this amide was secured, m.p. 116–116.5° after recrystallization from benzene-petroleum ether.

Anal. Calc'd for $C_{17}H_{19}NO_2$: C, 75.8; H, 7.1. Found: C, 75.9; H, 6.9.

Acyl migration N → O. To 3.077 g. (0.0126 mole) of this amide in 30 cc. of absolute ethanol was added 3.64 cc. (0.0175 mole) of 4.8 *N* hydrogen chloride in absolute ethanol and the whole was evaporated *in vacuo* after twenty minutes. The crystalline product (2.958 g., m.p. 193–197°) was recrystallized from absolute alcohol. It was identical with O-benzoyl-*dl*-ψ-ephedrine hydrochloride.

Anal. Calc'd for $C_{17}H_{20}ClNO_2$: C, 66.75; H, 6.6. Found: C, 66.1; H, 6.4.

Acyl migration O → N. To 2.49 g. (0.0084 mole) of this hydrochloride in 40 cc. of water, 5 *N* sodium hydroxide was added; 2.08 g. (91.7%) N-benzoyl-*dl*-ψ-ephedrine was thus obtained, m.p. 116.5°.

N-Benzoyl-dl-ephedrine. To a stirred solution of 2.47 g. (0.015 mole) of *dl*-ephedrine in 44 cc. of 0.5 *N* hydrochloric acid maintained at 40–50° were added, first, 1.8 cc. (0.0154 mole) of benzoyl chloride in 2 cc. of benzene, and subsequently 10 cc. of 20% sodium hydroxide. The yield was 3.7 g. (91.8%) of N-benzoyl-*dl*-ephedrine, m.p., 109–110°, after recrystallization from benzene petroleum ether.

Anal. Calc'd for $C_{17}H_{19}NO_2$: C, 75.8; H, 7.1. Found: C, 75.6; H, 7.2.

Experiments on acyl migrations. (*a*). To a solution of 1.35 g. (0.0052 mole) of N-benzoylephedrine in 10 cc. of anhydrous ethanol was added 1.56 cc. (1.5 moles per mole) of 4.8 *N* HCl in ethanol and the solution was evaporated at 25° after 20 minutes. The sirupy residue crystallized on standing for a few days in a desiccator. After treatment with 10 cc. of water, the crystals were filtered off; they consisted of 0.8784 g. (65%) of the starting material, m.p. 105–109°. The filtrate was evaporated *in vacuo* to dryness, the sticky residue was heated with 10 cc. of benzene and the mixture was filtered. The crystals, 0.353 g., showed m.p. 192–197°; they were identical with O-benzoyl-*dl*-ψ-ephedrine hydrochloride.

(*b*). N-benzoyl-*dl*-ephedrine (0.538 g.) was dissolved in 5 cc. of absolute alcohol, 0.5 cc. of 4.1 *N* HCl in absolute alcohol was added, and, after 15 minutes, the solution was evapo-

rated to dryness at 25° *in vacuo*. The sirupy residue was taken up in 2 cc. of absolute alcohol, and evaporated again. The now crystalline residue was first extracted with 15 cc. of cold water, then with 10 cc. of warm water; the undissolved part weighed 0.4722 g. (87%); m.p. 108–110°, alone and mixed with N-benzoylephedrine. The aqueous solution was evaporated; the crystalline residue (0.0258 g.) did not show a sharp m.p. (150–175°).

(*c*). On allowing 0.538 g. of the benzoyl derivative to react with 2 molecular proportions (0.978 cc.) of 4.1 *N* HCl in absolute alcohol, and working up the mixture exactly as described under (*b*), 0.4424 g. (82%) of unchanged benzoylephedrine, m.p. 108–110°, was recovered; 0.056 g. underwent acyl migration.

Attempts to separate N-benzoyl-dl-ephedrine from N-benzoyl-dl-ψ-ephedrine. (*a*). A mixture consisting of 2.69 g. (0.0105 mole) of each diastereoisomer was dissolved in 20 cc. of absolute alcohol, and 5.37 cc. of 5.6 *N* hydrogen chloride (0.0301 mole) in absolute alcohol was added. After 20 minutes, the solvent was removed at 25°, under 18 mm. pressure, and the sirupy residue was treated with a few cc. of absolute ethanol, then kept for several days in a desiccator until it became solid and no more traces of hydrochloric acid could be observed. To the crystals 40 cc. of cold water was added; filtration of the mixture yielded a crop of O-benzoyl-*dl*-ψ-ephedrine hydrochloride which weighed, after washing with 40 cc. of water, 2.899 g.; m.p. 195–199°. The filtrate, on concentrating to half of its volume, yielded a further crop, 1.365 g.; m.p. 195–198°. The dry residue weighed 1.675 g., m.p. as above. Total yield, 5.89 g. (99.8% based on the mixture of the benzoylated diastereoisomers). The excess of hydrogen chloride therefore exerted in the course of several days a configurational change in benzoylephedrine prior to acyl migration. The hydrochloride thus obtained was converted into N-benzoyl-*dl*-ψ-ephedrine by dissolving it in 50 cc. of water and treating with 5 *N* sodium hydroxide. The product, 5.05 g., showed m.p. 105–112°. After recrystallization from benzene and petroleum ether the m.p. rose to 116–116.5°, alone and in admixture with N-benzoyl-*dl*-ψ-ephedrine.

(*b*). To a solution of 0.538 g. of N-benzoyl-*dl*-ephedrine and 0.538 g. of N-benzoyl-*dl*-ψ-ephedrine in 10 cc. of absolute alcohol, 1 cc. of 4 *N* HCl in absolute ethanol was added and the mixture was kept for 15 minutes at room temperature. The solvent was then removed under reduced pressure at 25°, and the sticky residue was dissolved in a few cc. of absolute alcohol. On evaporating again, a partly crystalline residue resulted, which was extracted with 20 cc. and subsequently with 15 cc. of cold water. The undissolved crystals weighed 0.4398 g. (91%), and were identical with N-benzoyl-*dl*-ephedrine. The aqueous solution afforded on evaporation 0.6214 g. (102%) of O-benzoyl-*dl*-ψ-ephedrine hydrochloride, m.p. 197–200°.

(*c*). To a solution of 1.35 g. (0.0052 mole) of N-benzoyl-*dl*-ephedrine and 1.35 g. of N-benzoyl-*dl*-ψ-ephedrine in 10 cc. of absolute alcohol, 1.1 cc. of 4.7 *N* hydrogen chloride (0.0052 mole) in absolute alcohol was added. After 20 minutes the solvent was evaporated at 25° and 18 mm. pressure, and the residue was taken up in 2–3 cc. of absolute ethanol and evaporated again. The crystalline residue was dried over calcium chloride overnight, then triturated with 30 cc. of water, filtered, and washed with 30 cc. of water. The undissolved portion weighed 1.3 g. (96%); m.p. 104–107°, also in admixture with N-benzoyl-*dl*-ephedrine; mixed m.p. with N-benzoyl-*dl*-ψ-ephedrine: 85–95°. The aqueous filtrate afforded on evaporation 1.48 g. (96%) of the hydrochloride of O-benzoyl-*dl*-ψ-ephedrine, m.p. 195–197°.

C. *Derivatives of 1,2-diphenyl-2-aminoethanol. dl-1,2-Diphenyl-2-acetamidoethanol. dl-*1,2-Diphenyl-2-aminoethanol was prepared from benzoin oxime (10). From 0.5 g. of the amino alcohol and 0.28 g. of acetic anhydride in 9 cc. of dry pyridine at room temperature was obtained 0.523 g. (98.9%) of the amide, m.p. 196–197° (11a).

Attempt to effect acyl migration. To 0.3 g. (0.0012 mole) of the amide in 25 cc. of anhydrous ethanol, was added 0.35 cc. (0.0018 mole) of 5 *N* hydrogen chloride and the solution was kept for three days at room temperature. Evaporation of the solvent furnished 0.295 g. of product insoluble in water, m.p. 196°, identical with the starting material. Acyl migration therefore did not occur.

Conversion of dl-1,2-diphenyl-2-aminoethanol into its diastereoisomer. A solution of 5 g. of the hydrochloride of the amino alcohol in 150 cc. of hydrochloric acid (25 g. HCl per 100 cc. of water) was refluxed for twenty hours, decolorized with charcoal, and evaporated to dryness. The white crystalline residue was dissolved in a few cc. of water, and then alkalized. The mixture of diastereoisomeric free bases so obtained (2.4 g.) melted at 110–140°.

Separation of the acetyl derivatives of dl-1,2-diphenyl-2-aminoethanol and dl-1,2-iso-diphenyl-2-aminoethanol. Two and four-tenths grams (0.011 mole) of the mixture of the diastereoisomers obtained above was dissolved in 40 cc. of dry pyridine, and 1.2 cc. (0.012 mole) of acetic anhydride was added. The resulting greenish solution was kept for 24 hours at 25°, then was evaporated *in vacuo* almost to dryness, and the product filtered off; yield, 2.3 g., m.p. 105–150°.

(*a*). To a solution of 1.66 g. (0.0065 mole) of this mixture in 40 cc. of absolute ethanol, 1.3 cc. of 5.5 *N* hydrochloric acid (0.0071 mole) in anhydrous alcohol was added and the mixture was worked up after 24 hours. After removal of the solvent *in vacuo* at 40–45°, the residue was treated with 75 cc. of boiling water. The undissolved part weighed 0.73 g., m.p. 165–172°, and consisted of *dl*-1,2-diphenyl-2-acetamidoethanol. After recrystallization from 3.5 cc. of ethanol, the yield amounted to 0.56 g., m.p. 192–194°. For analysis it was repeatedly recrystallized from ethanol; the m.p. rose to 198° (11a).

Anal. Calc'd for $C_{16}H_{17}NO_2$: C, 75.3; H, 6.7. Found: C, 75.15; H, 7.0.

The 75 cc. of aqueous filtrate gave on alkalization 0.69 g. of white crystals of *dl*-1,2-*iso*-diphenyl-2-acetamidoethanol. Recrystallization from benzene afforded 0.48 g. of crystals, m.p. 147–149°. After one more recrystallization, the m.p. rose to 155° (11b).

Anal. Calc'd for $C_{16}H_{17}NO_2$: C, 75.3; H, 6.7. Found: C, 75.1; H, 7.2.

(*b*). To a solution of 0.21 g. (0.0008 mole) of *iso*-acetamide and 0.21 g. of the acetamide (m.p. 192°) in 9 cc. of absolute alcohol-benzene (8:1), was added 0.41 cc. of 5.6 *N* HCl in absolute alcohol and the mixture was kept at room temperature for 24 hours. The separated colorless needles, 0.146 g., showed m.p. 192–196°. The hydrochloride of *dl*-1,2-*iso*-diphenyl-2-amino-1-acetoxyethane, obtained from a similar experiment, was recrystallized for analysis from absolute ethanol and formed white radial needles, m.p. 204–205° (11b).

Anal. Calc'd for $C_{16}H_{18}ClNO_2$: C, 65.8; H, 6.2. Found: C, 65.5; H, 6.5.

The evaporation of alcohol from the filtrate at 40° furnished a crystalline residue, which was extracted with three 10-cc. portions of hot water; the undissolved part weighed 0.196 g. (93%), was free of chlorine and had m.p. 196–197°, alone and mixed with 1,2-diphenyl-2-acetamidoethanol.

The previously obtained hydrochloride, 0.146 g., was dissolved in 30 cc. of water, then alkalized; the precipitated amide, 0.174 g. (83%), showed m.p. 146–147° and was identical with *dl*-1,2-*iso*-diphenyl-2-acetamidoethanol.

D. *Oxazoline derivatives from N-benzoyl-3,4-diethoxy-dl-nor-ψ-ephedrine.* (*a*). To 0.5 g. of the corresponding benzamide (1), was added 1.6 cc. of thionyl chloride; the mixture melted and became yellow with simultaneous evolution of hydrogen chloride. The whole was kept for three hours at room temperature, then 70 cc. of dry ether was added and the solution was allowed to stand at −5° to −10° for three days. The separated crystals were collected on a filter, washed with a few cc. of dry ether, then recrystallized from petroleum ether; yield, 0.3 g., m.p. 107°. The product contained ionic chlorine. The analytical data agree with those calculated for 2-phenyl-4-methyl-4,5-dihydro-5-(3,4-diethoxyphenyl)oxazole hydrochloride (IX).

Anal. Calc'd for $C_{20}H_{24}ClNO_3$: C, 66.4; H, 6.7. Found: C, 66.5; H, 6.8.

(*b*). Treatment of 0.5 g. of N-benzoyl-3,4-diethoxy-*dl*-norephedrine (1) exactly in the above described manner did not give rise to a crystalline salt. A reddish-brown oil was secured, which could not be crystallized from petroleum ether.

Acknowledgment. The authors wish to express their thanks to Dr. Margaret Kovács Oskolás for the microanalyses.

SUMMARY

A new method has been described for the separation of diastereoisomeric amino alcohols based upon the different reactivity of N-acylephedrines and N-acyl-ψ-ephedrines towards alcoholic hydrogen chloride. The latter series of compounds form salts of O-acylated amino alcohols, which because of their far greater solubility in water can be separated easily from the unchanged amides of ephedrine series. Acylated norephedrine, *dl*-ephedrine and 1,2-diphenyl-2-aminoethanol have been separated from their diastereoisomers by use of the method.

The different reactivities of the diastereoisomers (2, 1) is supposedly due to restricted rotation, in consequence of which the hydroxyl and acylamido groups are in proximity to each other only in the case of acylated ψ-ephedrines. New projection formulas have been proposed in view of these experimental facts. The configuration of ephedrine at the nitrogen bearing carbon atom remains to be settled (25).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

STUDIES IN THE QUINOLINE SERIES. IX. 4-SUBSTITUTED-8-AMINOQUINOLINES AND RELATED NAPHTHALENES[1]

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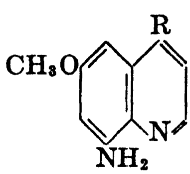
Since several of the 6-methoxy-8(alkylaminoalkylamino)lepidines prepared in connection with the antimalarial program (1, 2) have shown high antimalarial activity together with a toxicity much lower than that of the related quinolines, further work in this field seemed of interest.

As a part of this program, attempts were made to replace the 4-methyl group with other groups such as phenyl, carbethoxy, isopropyl, hydroxymethyl, and aldehyde, but considerable difficulty was experienced in obtaining the required 6-methoxy-8-amino-4-substituted quinolines, and in coupling them with the side chains.



I R = C_6H_5

II R = $COOC_2H_5$

III R = CH_2OH

IV R = CHO

V R = $CH(CH_3)_2$

6-Methoxy-4-phenyl-8-aminoquinoline (I) was prepared by condensing *beta*-chloropropiophenone with *p*-methoxy-*o*-nitroaniline, and reducing the nitroquinoline catalytically or with stannous chloride. The *beta*-chloropropiophenone required for this synthesis was originally prepared by the procedure of Allen and Barker (3), but as the yields were variable, and the reaction was frequently very vigorous, a modification was developed which avoided some of these difficulties. When *beta*-chloropropiophenone was condensed with *p*-methoxy-*o*-nitroaniline by the procedure used by Elderfield and co-workers (4) for the analogous 2-phenyl derivative, the yield of I was only 5–8%; this yield was raised to 30% by the use of Cellosolve as solvent. Attempts to couple I with 5-isopropylaminopentyl chloride by the usual procedure (5) failed to give an appreciable amount of product, and work on this phase had to be abandoned because the experimenter became allergic to *beta*-chloropropiophenone.

6-Methoxy-8-nitrolepidine was the starting material for the synthesis of II and for attempted synthesis of III, IV and V. The nitrolepidine was oxidized to the corresponding cinchoninic acid by the procedure of Turner, Mills, and Cope (6); this acid was then esterified and the ester reduced to give II. When II was

[1] Previous paper in this series, Campbell *et al.*, *J. Am. Chem. Soc.*, **69**, 1465 (1947).

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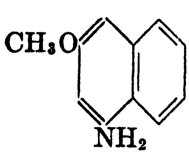
treated with Noval bromide or 1-isopropylamino-5-chloropentane the product was an oil which could not be distilled and from which we were unable to obtain any crystalline salt. Better results were obtained with diethylaminoethyl bromide, but as the product had no appreciable antimalarial activity no further efforts were made to prepare other drugs in this series.

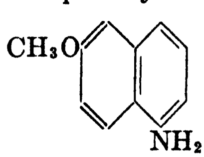
6-Methoxy-8-nitrolepidine was oxidized to the aldehyde by selenium dioxide, but all attempts to reduce 6-methoxy-8-nitrocinchonaldehyde to the amino alcohol (III), the amino aldehyde (IV) or the nitro alcohol gave only tars. It was hoped to prepare 6-methoxy-8-amino-4-isopropylquinoline (V) from 6-methoxy-8-nitrolepidine by condensation with formaldehyde followed by reduction. Although lepidine and 6-methoxylepidine react with formaldehyde to form the dimethylol compounds in good yields (7, 8) we were unable to isolate any appreable amount of methylol derivative from 6-methoxy-8-nitrolepidine, using aqueous formaldehyde, trioxane or paraformaldehyde.

A second phase of the work involved the attachment of other side chains to the 6-methoxy-8-aminolepidine nucleus. Alving (9) has found that 6-methoxy-8-(3′-isopropylaminopropylamino)lepidine is devoid of the Plasmocid type of toxicity so characteristic of most of the 8-aminoquinolines with short side chains; it therefore became of interest to prepare other 8-aminolepidines with short side chains. 6-Methoxy- and 6-hydroxy-8-(3′-*sec.*-butylaminopropylamino)lepidines were prepared, therefore, and the analogous quinolines without the 4-methyl group were also made for comparison. These syntheses were carried out in the usual way and presented no difficulties. 6-Methoxy-8-[bis-(dimethylaminomethyl)methylamino]lepidine was also desired for testing; 1,3-bis(dimethylamino)-2-propanol was prepared in excellent yield from dimethylamine and epichlorohydrin and converted to the chloro and bromo derivatives, but neither of these could be coupled with 6-methoxy-8-aminolepidine.

A third phase of the work was concerned with the preparation of naphthalene analogs of the 4- and 8-aminoquinolines. We originally planned to attach aminoalkylamino side chains to 3-methoxy-1-aminonaphthalene (VI) and to 6-methoxy-1-aminonaphthalene (VII), but we were not able to develop a satisfactory synthesis for VI in quantity. VII was readily prepared by a slight

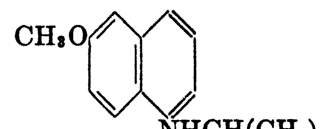


VI



VII

VIII



IX

modification of the procedure of Butenandt and Schramm (10). This nucleus

coupled readily with alkylaminoalkyl halides to give very good yields of the drugs, but as these products showed very slight antimalarial activity an extensive series was not made. Attempts to couple VII with 1,3-bis-(dimethylamino)-2-bromopropane were unsuccessful, and when the *p*-toluenesulfonate ester of 1,3-bis-(dimethylamino)-2-propanol was used the product was not the expected drug VIII, but may have been 6-methoxy-1-isopropylaminonaphthalene (IX). The mechanism by which the two dimethylamino groups were lost is obscure.

The antimalarial activities of the drugs prepared in this work are given in Table I. The authors wish to thank the Eli Lilly Company for carrying out the tests, and for the financial support which made this work possible.

TABLE I

ANTIMALARIAL ACTIVITY

COMPOUND	QUININE EQUIVALENTS TEST I-5
8-(3′-*sec.*-Butylaminopropylamino)-6-hydroxyquinoline	Q = 4
8-(3′-*sec.*-Butylaminopropylamino)-6-hydroxylepidine	Q = 0.16i
6-Methoxy-8-(3′-*sec.*-butylaminopropylamino)quinoline	Q = 0.16
6-Methoxy-8-(3′-*sec.*-butylaminopropylamino)lepidine	Q = 80
1-(4′-Isopropylamino-1′-methylbutylamino)-6-methoxynaphthalene	Q = 0.16i
1-(5′-Isopropylaminopentylamino)-6-methoxynaphthalene	Q = 0.16i
Ethyl 8-(2′-diethylaminoethylamino)-6-methoxycinchoninate	Q = 0.16i

EXPERIMENTAL[4,5]

beta-Chloropropiophenone. This material was prepared by a modification of the procedure of Allen and Barker (3). A mixture of 50 g. of *beta*-chloropropionic acid (11) and 45 g. of phosphorus trichloride was refluxed on a water-bath for 90 minutes, cooled, diluted with 200 ml. of dry benzene and decanted into a one-liter, three-neck flask fitted with a sealed stirrer and a reflux condenser which was protected by a calcium chloride drying tube. Seventy-five grams of anhydrous aluminum chloride was added in small portions over a period of two hours, each addition being accompanied by the evolution of heat and hydrogen chloride. The solution remained light yellow in color until addition was nearly complete, at which point a deep red color developed. When addition was completed the reaction mixture was refluxed on a water-bath for one hour, cooled, and poured into ice with good stirring. The organic layer was separated, washed with 100 ml. of water, dried over calcium chloride, and the benzene evaporated in a stream of dry air without the application of heat; the yield was 65.3 g. or 85% of a white solid, m.p. 46–48°. This product was recrystallized by dissolving in Skellysolve "B" at room temperature, cooling to 0° and filtering off the white plates, m.p. 47–48°.

4-Phenyl-6-methoxy-8-nitroquinoline. A mixture of 57.0 g. of 2-nitro-4-methoxyaniline, 51.0 g. of arsenic pentoxide, 51.0 g. of zinc chloride and 700 ml. of concentrated hydrochloric acid was heated on a steam-bath and a solution of 110 g. of *beta*-chloropropiophenone dissolved in 215 ml. of Cellosolve was added dropwise with stirring over a period of five hours. Heating and stirring were continued for one hour longer. Tetrachloroethane

[4] All melting points are uncorrected. The melting points of all salts were determined in sealed tubes and the samples were placed in the melting point block at room temperature.

[5] All analyses for C, H, and N were performed by Mr. Charles Beazley, Micro-Tech Laboratory, Skokie, Illinois.

(200 ml.) was added and the reaction mixture was allowed to cool and separate into two layers. The aqueous layer was decanted, the tarry organic layer was washed with two 100-ml. portions of concentrated hydrochloric acid and the combined acid solutions were then diluted with water to 9–10 times their original volume and allowed to stand overnight. The long, reddish needles which precipitated were recrystallized from 95% ethyl alcohol. Yield 24.0 g. or 30%; m.p. 129–134°. Repeated recrystallization from 95% ethanol yielded light tan needles, m.p. 133.5–135°.

Anal. Calc'd for $C_{16}H_{12}N_2O_3$: C, 68.56; H, 4.24; N, 10.00.
Found: C, 68.02; H, 4.15; N, 10.20.

4-Phenyl-6-methoxy-8-aminoquinoline. (A) *By reduction with stannous chloride.* A solution of 16.9 g. of stannous chloride dihydrate in 50 ml. of concentrated hydrochloric acid was cooled to 5° and a solution of 5.0 g. of 4-phenyl-6-methoxy-8-nitroquinoline in 40 ml. of concentrated hydrochloric acid was added dropwise, with stirring, over a period of one hour. The reaction mixture was then stirred at 0–5° for one hour and at room temperature for 90 minutes. Sodium hydroxide (40%) was added to strong alkalinity while the temperature was kept below 20°; at this point the tin salt was completely dissolved. The product, a dark brown solid, was collected and dried *in vacuo;* yield 5.6 g. (theoretical yield 4.5 g.), but combustion tests indicated the presence of inorganic salts. Distillation of this solid gave 3.2 g. (67%) of an extremely viscous, pale yellow oil, b.p. 178–192°/0.1 mm., which solidified on trituration with hexane and then had m.p. 74–77°. This product gave a negative Beilstein test indicating that no nuclear chlorination had occurred on treatment with stannous chloride.

Anal. Calc'd for $C_{16}H_{14}N_2O$: C, 76.83; H, 5.62; N. 11.17.
Found: C, 76.32; H, 5.54; N, 11.33.

(B) *By catalytic hydrogenation.* A solution of 5.6 g. (0.02 mole) of 4-phenyl-6-methoxy-8-nitroquinoline in 60 ml. of anhydrous ethyl acetate and 20 ml. of absolute ethanol was shaken with Raney nickel at room temperature under 3 atmospheres of hydrogen. The theoretical amount of hydrogen was absorbed in one hour. The residue was a dark, very viscous oil which on trituration with hexane crystallized to a gray solid, m.p. 71–74°; yield 4.4 g. or 88%.

Ethyl 6-methoxy-8-nitrocinchoninate. The 6-methoxy-8-nitrocinchoninic acid used in this work was prepared by the method of Turner, Mills, and Cope (6). A mixture of 54.0 g. of 6-methoxy-8-nitrocinchoninic acid, 800 ml. of anhydrous benzene, and 200 ml. of freshly distilled thionyl chloride was heated to reflux on a water-bath for six hours and was allowed to stand overnight. A total of 500 ml. of absolute ethanol was added through the top of the condenser in small portions with shaking. After the spontaneous reaction had subsided, the reaction mixture was refluxed on a water-bath for three hours, cooled, and filtered to remove a small amount of insoluble material. The filtrate was evaporated to dryness under reduced pressure with heating on a water-bath. Recrystallization of the residue from 95% ethyl alcohol yielded 46.0 g. or 76% of a light tan solid, m.p. 133–134°. Treatment of a small portion with decolorizing charcoal followed by two recrystallizations from 95% ethyl alcohol yielded fine, pale yellow needles, m.p. 142°.

Anal. Calc'd for $C_{13}H_{12}N_2O_5$: C, 56.52; H, 4.38; N, 10.14.
Found: C, 56.89; H, 4.00; N, 9.93.

Ethyl 6-methoxy-8-aminocinchoninate. A mixture of 37.5 g. (0.14 mole) of ethyl 6-methoxy-8-nitrocinchoninate, 32.0 g. of iron filings (Eastman Kodak, 40 mesh), 600 ml. of water, and 20 ml. of glacial acetic acid was stirred on a water-bath for fourteen hours, cooled, and filtered. The filter cake was leached out with 500 ml. of boiling dioxane and filtered while hot. Evaporation of the solvent under reduced pressure at 50° yielded a reddish-orange solid. No appreciable amount of product was obtained on further extraction of the filter cake. After one crystallization from 95% ethyl alcohol there was obtained 22.6 g. or 68% of an orange solid, m.p. 99–102°. This compound distilled at 162–167°/0.15 mm. to yield a clear red oil which soon solidified to yellow crystals, m.p. 108–109°.

Anal. Calc'd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38.

Found: C, 62.8; H, 5.49; N, 11.46.

Ethyl 6-methoxy-8-(2'-diethylaminoethylamino)cinchoninate. A solution of 24.6 g. (0.1 mole) of ethyl 6-methoxy-8-aminocinchoninate and 13.0 g. (0.05 mole) of *beta*-diethylaminoethyl bromide hydrobromide in 75 ml. of absolute ethanol was heated to reflux for 48 hours. The alcohol was removed under reduced pressure with a minimum of warming in a water-bath. The residue, a viscous dark red oil, was stirred vigorously with 200 ml. of cold water and the yellow solid which separated was collected. It proved to be 7.6 g. of unchanged ethyl 6-methoxy-8-aminocinchoninate, m.p. 102–104°. The filtrate was extracted with 100-, 100-, and 50-ml. portions of chloroform and the combined extracts were dried over potassium carbonate. The dark red residue remaining after evaporation of the solvent was distilled under vacuum to give an oil, (b.p. 200–215°/0.4 mm.) which was dissolved in 30 ml. of ice-cold 6 *N* hydrochloric acid. The acid solution was extracted with three 100-ml. portions of ether and the aqueous layer was slowly neutralized in the cold by the addition of solid potassium carbonate. When the evolution of carbon dioxide had ceased, 10% sodium hydroxide solution was added to *p*H 10. The cold solution was extracted rapidly with three 100-ml. portions of ether and the combined extracts were dried over potassium carbonate. After removal of the drying agent the solution was chilled in an ice-bath and treated with a saturated ethereal solution of anhydrous oxalic acid which was added dropwise from a burette with vigorous stirring. It was found essential to add the oxalic acid solution very slowly and to avoid the presence of an excess at any time in order to isolate a stable salt. When precipitation was complete the orange-yellow solid was collected and dried *in vacuo*. Recrystallization from absolute ethanol yielded 6.0 g. or 28% of orange-yellow plates, m.p. 146–147°. On analysis this salt proved to be a monooxalate.

Anal. Calc'd for $C_{21}H_{29}N_3O_7$: C, 58.05; H, 6.50; N, 9.67.

Found: C, 58.28; H, 6.69; N, 9.52.

6-Methoxy-8-nitrocinchoninaldehyde. A mixture of 60.0 g. of 6-methoxy-8-nitrolepidine, 46.0 g. of freshly prepared and sublimed selenium dioxide, 400 ml. of chlorobenzene, and 100 ml. of glacial acetic acid was refluxed for 48 hours and filtered from the selenium metal while still hot. The filtrate was evaporated to dryness at the water-pump with a minimum of heating. The residue, a reddish solid, was dissolved in 500 ml. of dioxane, refluxed with decolorizing charcoal and filtered hot through a mat of Hyflo Super-Cel. On cooling, a light tan solid, m.p. 183–185°, (50.4 g., 79%) separated from the filtrate. A small sample was recrystallized three times from dioxane and once from a 1:1 mixture of dioxane and 95% ethyl alcohol. The product was an almost colorless, fluffy solid which melted at 192°, decolorized potassium permanganate solution and gave an addition compound with sodium bisulfite.

Anal. Calc'd for $C_{11}H_8N_2O_4$: C, 56.90; H, 3.47; N, 12.07.

Found: C, 57.46; H, 3.53; N, 11.96.

1-sec.-Butylamino-3-propanol. A solution of 100 g. (1.05 moles) of trimethylene chlorohydrin and 200 g. (2.7 moles) of *sec.*-butylamine in 300 ml. of benzene was heated in an iron bomb for 9 hours. The residue remaining after removal of the benzene was treated with a solution of 42 g. of sodium hydroxide in 50 ml. of water and extracted with two 500-ml. portions of ether. The combined extracts were dried over potassium carbonate, the ether removed and the residue distilled to give 108 g. or a 78% yield of a colorless oil, b.p. 105°/20 mm., n_D^{20} 1.4490.

1-sec.-Butylamino-3-bromopropane hydrobromide. The method described by Campbell and co-workers (11) for the preparation of 1-alkylamino-6-bromohexanes from the corresponding amino alcohols was found to be very satisfactory. The yield of light tan crude material was 85%. After one recrystallization from ethanol and ether the product was a colorless, crystalline solid, m.p. 189–190° (dec.).

Anal. Calc'd for $C_7H_{17}Br_2N$: C, 30.57; H, 6.23; N, 5.09.

Found: C, 30.60; H, 6.02; N, 4.98.

6-Methoxy-8-(3'-sec.-butylaminopropylamino)quinoline. A mixture of 34.8 g. (0.20 mole) of freshly distilled 6-methoxy-8-aminoquinoline, 27.5 g. (0.10 mole) of 1-*sec.*-butyl-

amino-3-bromopropane hydrobromide and 300 ml. of absolute ethanol was refluxed for 48 hours, cooled, and filtered to remove the precipitated 6-methoxy-8-aminoquinoline hydrobromide. The filtrate was concentrated to a small volume under reduced pressure and was poured into a solution of 30 ml. of concentrated hydrochloric acid in 210 ml. of water. The acid solution was chilled in an ice-bath and sodium hydroxide pellets were added slowly, with stirring, to strong alkalinity. The solution was extracted with 100- and 50-ml. portions of chloroform and the combined extracts were dried over magnesium sulfate. After removal of the chloroform the dark, viscous residue was distilled from a 50-ml. Claisen flask with a low, wide side arm to give 15.4 g. (53%) of a viscous, red oil, b.p. 170–173°/0.08 mm. The oil was dissolved in 25 ml. of *n*-propanol and titrated with a slight excess of the amount of 2.017 *N* propanolic hydrogen chloride required to form the dihydrochloride. The yellow salt precipitated on cooling. After one recrystallization from ethanol and ether this material melted at 207.5–208.5° (dec.). It analyzed as a hemihydrate.

Anal. Calc'd for $C_{17}H_{25}N_3O \cdot 2HCl \cdot \frac{1}{2}H_2O$: C, 55.28; H, 7.64; N, 11.38.
Found: C, 55.60; H, 7.48; N, 11.67.

6-Methoxy-8-(3'-sec.-butylaminopropylamino)lepidine. This was prepared as described above using 17.9 g. (0.065 mole) of 1-*sec.*-butylamino-3-bromopropane hydrobromide, 24.4 g. (0.13 mole) of 6-methoxy-8-aminolepidine, and 200 ml. of absolute ethanol. There was obtained 9.2 g. (47%) of a viscous red oil, b.p. 180–184°/0.03 mm., which was converted to the dihydrochloride in propanol. The orange-yellow salt, m.p. 219–220° (dec.), analyzed as a hemihydrate.

Anal. Calc'd for $C_{18}H_{27}N_3O \cdot 2HCl \cdot \frac{1}{2}H_2O$: C, 56.39; H, 7.89; N, 10.96.
Found: C, 56.10; H, 7.77; N, 11.09.

6-Hydroxy-8-(3'-sec.-butylaminopropylamino)lepidine. A solution of 11.2 g. (0.037 mole) of 6-methoxy-8-(3'-*sec.*-butylaminopropylamino)lepidine in 100 ml. of constant boiling 48% hydrobromic acid was heated at 110° ± 2° (inside temperature) in a current of nitrogen for three and one-half hours. The reaction mixture was cooled to 15° in an ice-bath and 25% sodium hydroxide solution was added, under an atmosphere of nitrogen, to *p*H 9.5. The product separated as a dark red tar which adhered to the sides of the flask. The aqueous phase was decanted and the residual tar was dissolved in 20 ml. of absolute ethanol. Acidification with propanolic hydrogen chloride followed by the addition of ether precipitated the hydrochloride as a red oil, which was triturated with four successive portions of acetone to remove the last traces of water. After extensive scratching under anhydrous ether the oil was induced to crystallize to a yellow solid, m.p. 194–196° (dec.) after softening at 186–188°; the yield of crude material 7.9 g. or 54%. Recrystallization from methanol and ether raised the melting point to 200–202° (dec.), but the material was still contaminated with inorganic salts. It was therefore dissolved in the minimum amount of water, neutralized with solid sodium carbonate and extracted with chloroform. The dried chloroform extract was acidified with a slight excess of propanolic hydrogen chloride, and the addition of ether precipitated the yellow hydrochloride, m.p. 220–222° (dec.). This derivative was free from ash and analyzed as the dihydrochloride hemihydrate.

Anal. Calc'd for $C_{17}H_{25}N_3O \cdot 2HCl \cdot \frac{1}{2}H_2O$: C, 55.28; H, 7.64; N, 11.38.
Found: C, 55.26; H, 7.51; N, 11.30.

8-(3'-sec.-Butylaminopropylamino)-6-quinolinol. A solution of 12.0 g. of 6-methoxy-8-(3'-*sec.*-butylaminopropylamino)quinoline dihydrochloride hemihydrate in 100 ml. of constant boiling 48% hydrobromic acid was heated at 110° ± 2° for three hours in a stream of nitrogen. When the reaction mixture was allowed to cool slowly the product separated as fine, light tan needles which were collected and washed thoroughly with acetone and anhydrous ether; yield 13.0 g. or 77%; m.p. 207–208° (dec.). Analysis showed the salt to be a trihydrobromide.

Anal. Calc'd for $C_{16}H_{23}N_3O \cdot 3HBr$: C, 37.23; H, 5.08; N, 8.14.
Found: C, 37.23; H, 5.10; N, 8.42.

5-Acetylamino-2-naphthol. This compound was prepared in 42% yield by the procedure of Butenandt and Schramm (10). By the procedure described below yields as high as 82%

were obtained. The fusion pot was a stainless steel beaker (7.8 cm. in diameter and 11.2 cm. deep) equipped with a removable stainless steel cover and fitted with a stainless steel propellor type stirrer and powerful motor. The pot was charged with 140 g. of potassium hydroxide pellets and 10 ml. of water and was heated to 250° in a Wood's metal-bath. Sixty grams of 1-naphthylamine-6-sulfonic acid (Cleve's acid, duPont technical grade) was added in three portions and the mass was heated rapidly to 310° and maintained at 310–320° for no longer than eight minutes and for an even shorter period if the odor of ammonia became apparent above the fusion pot before that time. The melt was cooled and dissolved in 250 ml. of boiling water. The results of three fusions were combined, made strongly acid to pH paper with ice cold 6 *N* hydrochloric acid and filtered. The filter cake was leached out with a solution of 70 ml. of concentrated hydrochloric acid in 1000 ml. of water and filtered. This process was repeated four times, at which point the insoluble residue was small and tarry in nature. The combined filtrates were cooled and potassium hydroxide pellets were added to turbidity. A saturated solution of ammonium carbonate was then added until no more precipitate formed. The brown solid was collected and dried in a vacuum desiccator overnight. Acetic anhydride (300 g.) was added cautiously to the slightly moist material (160 g.) which was cooled in an ice-bath. After the initial mildly exothermic reaction had subsided, the mixture was stirred at room temperature for 3 hours and the light tan solid collected and dried in air; yield 134 g. or 82%, m.p. 211–213°.

6-Methoxy-1-naphthylamine. This was prepared from 5-acetylamino-2-naphthol by the procedure of Butenandt and Schramm (10). These workers report m.p. 205–220° (dec.) for 6-methoxy-1-naphthylamine hydrochloride and m.p. 74° for the free base. Wilds and Close (12) report m.p. 255° (dec.) for the hydrochloride. The crude hydrochloride obtained in this work melted at 230–239° (dec.) and the free base melted 64–66°.

1-(5'-Isopropylaminopentylamino)-6-methoxynaphthalene. A mixture of 23.0 g. (0.133 mole) of 6-methoxy-1-naphthylamine, 12.2 g. (0.066 mole) of 1-isopropylamino-5-chloropentane hydrochloride, and 15 ml. of water was stirred and heated in an oil-bath at 85–90° for 20 hours and at 100° for an additional 4 hours. The hot reaction mixture was poured into a solution of 25 ml. of concentrated hydrochloric acid in 100 ml. of water. After cooling, the purple crystals of recovered 6-methoxy-1-naphthylamine hydrochloride were collected, the filtrate was chilled in an ice-bath and sodium hydroxide pellets were added to strong alkalinity. The basic solution was then extracted with two 100-ml. portions of chloroform, the combined extracts were dried over magnesium sulfate, and the chloroform was evaporated under reduced pressure with mild warming. Distillation of the residue gave a pale yellow oil, b.p. 190–195°/0.18 mm.; yield 15.0 g. or 75%. The oil was dissolved in 40 ml. of *n*-propanol and treated with propanolic hydrogen chloride; the dihydrochloride was precipitated by the cautious addition of anhydrous ether. It had a slight greenish cast and the m.p. 214–216° (dec.). After one recrystallization from ethanol and ether this compound retained its pale green tint and melted at 216–218° (dec.).

Anal. Calc'd for $C_{19}H_{28}N_2O \cdot 2HCl$: C, 61.12; H, 8.12; N, 7.50.
Found: C, 60.70; H, 8.01; N, 7.52.

1-(4'-Isopropylamino-1'-methylbutylamino)-6-methoxynaphthalene. This was prepared in the same way, using 14.7 g. (0.085 mole) of 6-methoxy-1-naphthylamine, 12.5 g. (0.043 mole) of 1-isopropylamino-4-bromopentane hydrobromide, and 15 ml. of water; yield 6.8 g. or 53% of a viscous, pale yellow oil, b.p. 185–187°/0.15 mm. The dihydrochloride, prepared in propanol, precipitated as an oil on the addition of dry ether. It was crystallized with difficulty by scratching under successive portions of fresh ether. After drying *in vacuo* this compound had no melting point but began to decompose at 108°.

Anal. Calc'd for $C_{19}H_{28}N_2O \cdot 2HCl \cdot \frac{1}{2}H_2O$: C, 59.68; H, 8.17; N, 7.33.
Found: C, 59.46; H, 7.88; N, 6.83.

From mixtures of methanol, ethanol, or propanol and ether, the hydrochloride separated as an oil which could not be crystallized. Recrystallization from chloroform and ether yielded a yellow solid, m.p. 179–182° (dec.), which was shown by analysis to contain slightly

less than one molar equivalent of chloroform. Trituration with hexane followed by drying for 24 hours in a vacuum desiccator and for six hours in an Abderhalden pistol at 77° and 2 mm. failed to remove the chloroform.

1,3-Bis-(dimethylamino)-2-propanol. One mole (92.5 g.) of epichlorohydrin was added at the rate of 3–4 drops per second, with vigorous stirring, to 800 g. of 40% dimethylamine solution. The reaction was exothermic and the inside temperature had risen to 70° by the time addition was completed. The reaction mixture was stirred at 90° for 6 hours and then allowed to stand overnight. The mixture was chilled in an ice-bath and saturated with sodium hydroxide; the yellow organic layer which separated was dried over sodium hydroxide. Distillation through a short Vigreux column yielded 96.9 g. or 66% of a colorless oil, b.p. 82°/23 mm., 90°/32 mm., 98°/48 mm., n_D^{20} 1.4418, d_4^{20} 0.8788, MR_D (calc'd), 43.95; MR_D (obs.), 43.98; neutral equivalent (calc'd) 73.0; neutral equivalent (obs.), 73.3. The amino alcohol readily formed a dihydrochloride m.p. 255–257° (dec.), and a dihydrobromide, m.p. 228–230° (dec.).

1,3-Bis-(dimethylamino)-2-bromopropane hydrobromide. A solution of 66.5 g. (0.45 mole) of 1,3-bis-(dimethylamino)-2-propanol in 250 ml. of dry benzene was cooled below 10° and 97.0 g. (0.47 mole) of freshly distilled thionyl bromide was added dropwise with mechanical stirring over a period of two hours. When the addition was complete the mixture was stirred at 10° for 30 minutes and at room temperature for an hour. The cream colored solid was washed well with anhydrous ether and dried *in vacuo*. Yield 81.3 g. or 62%. An almost colorless solid, m.p. 187–189° (dec.) after softening at 167–169°. This material was hygroscopic and turned to an oil on exposure to the air for about 10 minutes.

Anal. Calc'd for $C_7H_{17}BrN_2 \cdot HBr$: C, 28.98; H, 6.25; N, 9.66.
Found: C, 28.82; H, 6.19; N, 9.28.

1,3-Bis-(dimethylamino)-2-propyl p-toluenesulfonate hydrochloride. A solution of 65.0 g. (0.34 mole) of *p*-toluenesulfonyl chloride in 300 ml. of chloroform was cooled in an ice-bath and 44.8 g. (0.31 mole) of 1,3-bis-(dimethylamino)-2-propanol was added over a period of 90 minutes while the temperature was kept below 20°. The mixture was stirred at room temperature for two hours after the addition was complete and was filtered. The product was somewhat oily in nature but crystallized well when stirred with anhydrous ether. After drying in a vacuum desiccator there was obtained 65.8 g. or 64% of a white powder. The analytical sample was recrystallized from ethanol and ether and was obtained as white plates, m.p. 166–167° (dec.). The product analyzed as a hemihydrate.

Anal. Calc'd for $C_{14}H_{25}N_2O_3S \cdot \frac{1}{2}H_2O$: C, 48.61; H, 7.58; N, 8.11.
Found: C, 48.50; H, 7.48; N, 7.62.

Reaction of 6-methoxy-1-naphthylamine with 1,3-bis-(dimethylamino)-2-propyl p-toluenesulfonate hydrochloride. A mixture of 21.0 g. (0.12 mole) of 6-methoxy-1-naphthylamine, 17.3 g. (0.05 mole) of 1,3-bis-(dimethylamino)-2-propyl *p*-toluenesulfonate hydrochloride hemihydrate, 150 ml. of chloroform, and 50 ml. of acetone was refluxed for 24 hours. The amine dissolved rapidly and the sulfonate ester formed a milky suspension. At the end of the heating period the milkiness had disappeared and a flocculent gray solid had separated. The gray solid was removed by filtration from the cold mixture; it proved to be largely unreacted *p*-toluenesulfonate. The filtrate was concentrated to a small volume and the residue was stirred vigorously with 10% sodium hydroxide solution. The dark organic layer was separated, the aqueous phase was extracted with two 50-ml. portions of chloroform and the combined organic layers were dried over magnesium sulfate. Distillation of the residue remaining after removal of the chloroform gave two fractions. The first one, b.p. 130–145°/0.4 mm., was a mixture which could not be separated into its components. The second fraction, b.p. 145–155°/0.45 mm., was a pale yellow oil (2.5 g.) which formed a hydrochloride m.p. 199–200° (dec.). Analysis showed that it was not the desired product but may have been 1-isopropylamino-6-methoxynaphthalene hydrochloride.

Anal. Calc'd for $C_{18}H_{27}N_3O \cdot 3HCl$: C, 52.62; H, 7.36; N, 10.23.
Calc'd for $C_{18}H_{27}N_3O \cdot 2HCl$: C, 57.75; H, 7.81; N, 11.23.

Calc'd for 1-isopropylamino-6-methoxynaphthalene hydrochloride, $C_{14}H_{17}NO \cdot HCl$: C, 66.79; H, 7.21; N, 5.57.

Found: C, 67.80; H, 6.99; N, 5.55.

SUMMARY

1. The synthesis of several 6-substituted-8-aminolepidines and related compounds has been described.
2. Some 6-methoxy-1-aminonaphthalene derivatives have also been prepared as possible antimalarials.
3. The antimalarial activities of these compounds have been determined.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF CLARK UNIVERSITY]

CARBOXYMETHYLATION OF AMINES. I. PREPARATION OF ETHYLENEDIAMINE TETRAACETIC ACID

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The reactions of cyanides and aldehydes with ammonia and with amines have been rather extensively investigated. The most well-known of these reactions is the Strecker Synthesis (1) which was first used by Strecker in 1850 but which has since been modified by other workers. A general reaction for the modified type of Strecker Synthesis is:

$$NH_4Cl + NaCN + RCHO \rightarrow R\overset{\overset{\displaystyle NH_2}{|}}{C}HCN + NaCl + H_2O$$

$$R\overset{\overset{\displaystyle NH_2}{|}}{C}HCN + 2H_2O + HCl \rightarrow R\overset{\overset{\displaystyle NH_2}{|}}{C}HCOOH + NH_4Cl$$

An example of this type of reaction has been described in detail by Kendall and McKenzie (2). One of the chief disadvantages of this method of preparation is the evolution of free hydrogen cyanide, which takes place on the addition of hydrochloric acid. This type of reaction has recently been extended to amines by Ulrich and Ploetz (3) who described the reaction of hydrogen cyanide and formaldehyde with ethylenediamine and other polyamines. The reaction may be illustrated schematically by the following equations:

$$CH_2O + HCN \rightarrow HOCH_2CN$$

$$4HOCH_2CN + H_2NCH_2CH_2NH_2 \rightarrow \begin{array}{c} NCCH_2 \qquad\qquad CH_2CN \\ \searrow \qquad\qquad \swarrow \\ NCH_2CH_2N \\ \swarrow \qquad\qquad \searrow \\ NCCH_2 \qquad\qquad CH_2CN \end{array} + 4H_2O$$

$$\begin{array}{c} NCCH_2 \qquad\qquad CH_2CN \\ \searrow \qquad\qquad \swarrow \\ NCH_2CH_2N \\ \swarrow \qquad\qquad \searrow \\ NCCH_2 \qquad\qquad CH_2CN \end{array} + 8H_2O \rightarrow \begin{array}{c} HOOCCH_2 \qquad\qquad CH_2COOH \\ \searrow \qquad\qquad \swarrow \\ NCH_2CH_2N \\ \swarrow \qquad\qquad \searrow \\ HOOCCH_2 \qquad\qquad CH_2COOH \end{array} + 4NH_3$$

Although the yields of intermediate nitriles are fairly high, the chief disadvantages of this synthesis for the preparation of alpha amino acids are the problem of handling large quantities of hydrogen cyanide gas and the difficulties in hydrolyzing the nitriles that are formed in the reaction.

In 1933, F. C. Bersworth (4), working with Dr. William H. Warren at Clark University, devised a method for producing alpha amino acids by treating solutions of aliphatic amines with alkali cyanides and an aliphatic aldehyde. This

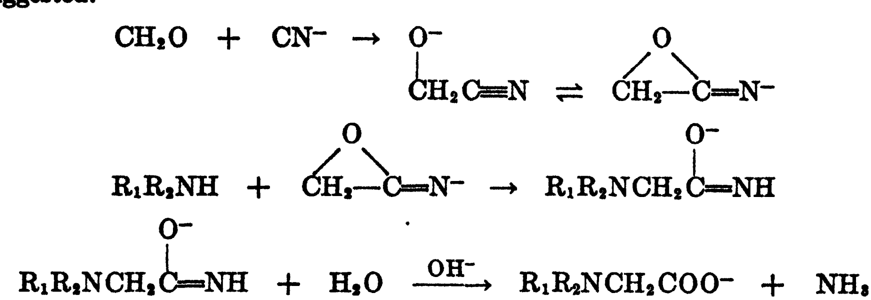
type of reaction is quite different, both in the conditions employed and in the results obtained, from the Strecker type of synthesis given above and has been subjected to considerable amount of investigation in the laboratories of Clark University. The commercial procedure for carrying on this reaction has been described by Bersworth (5). This is the first of a series of publications dealing with these reactions, which shall be called carboxymethylation of amines. It is the purpose of this paper to describe in some detail the optimum conditions and by-products obtained for the reaction of ethylenediamine with sodium cyanide and formaldehyde. There is also some consideration of the probable reaction mechanism but that is not the primary purpose of this report.

Some suggestion as to the course of the reaction may be obtained from the preliminary work done by Kohn (6) who first studied the reaction between potassium cyanide and formaldehyde and postulated the formation of a salt of glyconitrile according to the following reaction:

$$KCN + CH_2O \rightarrow KOCH_2CN$$

He tried to isolate the pure nitrile from the reaction of calcium cyanide with formaldehyde but was unsuccessful. Mutschen (7) showed that the nitrile is not appreciably decomposed at room temperature for fifty hours in solution and remains unchanged up to 100 hours in the presence of excess alkali. The pure glyconitrile was isolated by Polstorf and Meyer (8).

We have found that the nitrile decomposes rapidly at temperatures above 30°. Also, we have found that the reaction of an alkalized solution of glyconitrile with an amine produces a good yield of the amino acid. It seems probable, therefore, that it is an intermediate in the reaction. From information available at present, the following tentative course for a general carboxymethylation reaction is suggested.



where R_1 and R_2 represent hydrogen or alkyl groups. The evolution of the ammonia begins immediately and continues throughout the course of the reaction. It is therefore probable that the reaction does not involve the formation of the substituted alpha aminonitrile intermediate, as in the case of the reaction described by Ulrich and Ploetz (3), which takes place in neutral and acid solution. The possibility that the alkaline reaction takes place through the hydrolysis of glyconitrile to form a salt of glycollic acid was ruled out by Smith (9) who showed that alkaline solutions of glycollic acid do not react with ethylenediamine. In fact everything about the carboxymethylation reaction indicates that it is

radically different from the Strecker type of synthesis. One of the most striking characteristics of the new reaction is the fact that strongly alkaline conditions are necessary. High alkalinity seems to have two effects, both of which favor the reaction: first, the ammonia is driven off more rapidly and side reactions are thus prevented; and secondly, the presence of a strong base has a catalytic effect on the reaction (probably because it favors formation of the alcoholate ion of glyconitrile as is shown in the mechanism proposed above).

The usual method of producing ethylenediamine tetraacetic acid is the reaction of chloracetic acid or its salts with ethylenediamine. This usually produces a fair yield of the desired material but many by-products are formed.

Since the reaction of ethylenediamine with sodium cyanide and formaldehyde to form ethylenediamine tetraacetic acid has been carefully investigated, it is given here as a first example of carboxymethylation. The over-all reaction may be represented by the following equation:

$$H_2NCH_2CH_2NH_2 + 4NaCN + 4CH_2O + 4H_2O \rightarrow \begin{array}{c} NaOOCCH_2 \\ \diagdown \\ \end{array}\!\!\! \begin{array}{c} \\ NCH_2CH_2N \\ \\ \end{array}\!\!\! \begin{array}{c} CH_2COONa \\ \diagup \\ \end{array}$$

$$\begin{array}{ccc} NaOOCCH_2 & & CH_2COONa \\ & \diagdown \quad \diagup & \\ & NCH_2CH_2N & \quad + 4NH_3 \\ & \diagup \quad \diagdown & \\ NaOOCCH_2 & & CH_2COONa \end{array}$$

The reaction was first attempted by adding four consecutive molar amounts of sodium cyanide and formaldehyde to each mole of amine. The yields obtained in this way were very low. The reaction conditions were then varied by using a low temperature and by bubbling air through the reaction mixture to remove the ammonia as soon as it was produced. Under these conditions 25% of the theoretical amount of product was isolated. It was felt that the yield of the tetraacetic acid was much higher than 25%, however, since the by-products of the reaction formed a syrupy solution which seemed to inhibit crystallization of the amino acid.

Probably one of the chief difficulties with this reaction, when carried out in this manner, is the side reaction of ammonia with sodium cyanide and formaldehyde to form mono-, di-, and tri-glycine. This is due to carboxymethylation of the ammonia formed by hydrolysis of intermediate nitrile groups according to the following reaction:

$$NH_3 + {}^{-}OCH_2CN \rightarrow H_2NCH_2\overset{\displaystyle O^-}{\overset{|}{C}}{=}NH$$

Repetition of this step, together with hydrolysis, leads to the formation of sodium salts of glycine, diglycine, and triglycine. The formation of diglycine and triglycine from glyconitrile was demonstrated by Polstorf and Meyer (8). This suggested the possibility that the ammonia was not being removed fast enough and that a lower temperature should be used to hinder the rate of hydrolysis of the nitrile intermediate. It was also decided to add the reagents very slowly in order to keep the concentration of the nitrile as low as possible. The reaction, when carried out in this way, showed somewhat improved yields. When the evolution of ammonia was further increased by carrying on a slow distillation

under reduced pressure during the course of the reaction and by raising the *p*H of the solution through the addition of sodium hydroxide, the yield was finally raised to about 75% of the theoretical amount. No further modification of the conditions seemed to result in any further increase.

The detection of an appreciable amount of hexamethylenetetramine as by-product and the competing carboxymethylation of ammonia suggested the possibility that not enough formaldehyde and cyanide were present to completely substitute all the hydrogens of ethylenediamine. After carrying out the reaction as described above and the subsequent isolation of the desired tetraacetic acid, the mother liquor was treated with a fresh portion of sodium cyanide and formaldehyde under the same conditions. The isolation of an additional batch of ethylenediamine tetraacetic acid, indicated that some of the ethylenediamine was incompletely substituted. Accordingly, it was decided to run the reaction with an excess of sodium cyanide and formaldehyde under the optimum conditions described above. This resulted in yields of the desired product which amounted to as much as 96% of the theoretical amount. It is believed therefore that the problem of preparing this material has been adequately solved.

The industrial method outlined in the Bersworth patents (5) employs very high temperatures, is much more rapid and also gives high yields. It is not adapted to small-scale preparations, however, and when carried out in the laboratory often results in the formation of colored by-products.

The detailed procedure for the reaction is given under two sets of conditions in the experimental part. The identity and purity of the product was established by Dumas nitrogen determination, analysis of the dibarium salt, and *p*H titration curve.

The carboxymethylation reaction has been thoroughly investigated in this laboratory and extended to a large number of amines. These reactions will be reported in subsequent publications.

EXPERIMENTAL

Ethylenediamine tetraacetic acid. I. A one-liter, three-necked flask was equipped with a dropping-funnel, distilling-arm and condenser, and a glass stirrer fitted through a vacuum-tight rubber stopper. The stirrer was operated by an eccentric attached to a stirring motor directly above the rubber stopper, the under portion of which was hollowed out to allow free motion of the stirrer. In the reaction flask was placed 33.3 g. (0.333 mole) of a 60% solution of ethylenediamine, and to this was added a solution containing 81.5 g. (1.66 mole) of sodium cyanide and 7.0 g. of sodium hydroxide. The mixture was diluted to about 200 cc. and was brought to a temperature of 10° by means of a water-bath. 27.8 g. of a 36% solution (0.333 mole) of formaldehyde was diluted to 200 cc. and added continuously over a period of twenty hours. During this time the reaction mixture was stirred and maintained at a temperature of 10°. When all the formaldehyde had been added, the temperature was brought to 60° and the solution was distilled under vacuum until 200 cc. of distillate had been collected. The reaction mixture was then brought to a temperature of 16° while 100 cc. of a solution containing 0.166 mole of formaldehyde was added continuously over a period of eight hours. The mixture was vacuum distilled as before until 100 cc. of distillate had been collected. The process was continued with further additions of formaldehyde followed by distillation until 1.66 mole of formaldehyde had been added. The amounts added, time allowed for reaction, temperature, and quantity of water removed by distillation are shown in Table I.

The resulting product was a clear and nearly colorless solution. It was diluted to one liter and brought to a *p*H of 1.2 by the slow addition of 6 *M* sulfuric acid over a period of two hours with stirring. Stirring was then continued for two hours more to insure complete precipitation. The white crystalline product was filtered and washed twice with a little water. After it was dried in an oven at 110° for two hours, 93.3 g. (96% of the theoretical amount) of ethylenediamine tetraacetic acid was obtained.

Anal. Calc'd for $C_{10}H_{16}N_2O_8$: N, 9.58. Found: N, 9.50.

II. The following method is shorter and more convenient but results in somewhat reduced yields:

The reaction was carried out exactly as described above with the same concentrations of reagents but with the modifications in the conditions indicated below in Table II.

TABLE I

PREPARATION OF ETHYLENEDIAMINE TETRAACETIC ACID

REACTION TIME, HRS.	MOLES CH_2O ADDED	TEMP., °C	WATER REMOVED CC. DISTILLATE
20	0.333	10	200
8	.166	16	100
8	.166	16	100
6	.166	25	100
6	.166	25	100
4	.166	30	100
4	.166	30	100
4	.166	30	100
4	.166	30	200

TABLE II

PREPARATION OF ETHYLENEDIAMINE TETRAACETIC ACID BY SHORT METHOD

REACTION TIME, HRS.	MOLES CH_2O ADDED	TEMP., °C	WATER REMOVED CC. DISTILLATE
6	0.333	20	100
4	.333	25	100
4	.333	30	100
3	.333	35	100
3	.333	35	400

From the light reddish-brown solution obtained, the acid was isolated just as is described above. 76.5 g. (79% of the theoretical amount), of the amino acid was obtained.

Dibarium salt. Six g. of ethylenediamine tetraacetic acid was dissolved in 60 cc. of 0.40 *M* barium hydroxide to give a nearly clear solution. The solution was clarified by filtration and was mixed with 90 cc. more of the barium hydroxide solution. When the resulting solution was heated a heavy white mass of crystals of the dibarium salt precipitated. The crystals were decanted and washed several times by decantation, and then dried for three hours at 160°. The product was analyzed gravimetrically for barium by the sulfate method.

Anal. Calc'd for $C_{10}H_{12}Ba_2N_2O_8$: Ba, 48.90. Found: Ba, 48.81.

Glyconitrile. Seventy-three and one-half g. of sodium cyanide (1.5 mole) was dissolved in 200 cc. of water and was treated with 47.5 g. (1.58 moles) of formaldehyde while the solution was cooled by direct addition of ice. After it was allowed to stand for five minutes the solution was slowly made acid with 200 cc. of 7.82 *N* sulfuric acid. The temperature was kept down during this process by further additions of ice. 10 g. of dry sodium carbonate

was then added to bring the pH of the solution to approximately 6.0. A sample of this solution was extracted with ether several times. Evaporation of the ether extracts resulted in the formation of a colorless liquid. Various tests performed on this material showed that it behaved like glyconitrile as described in the literature.

Action of sodium salt of glyconitrile on ethylenediamine. In a 1000-cc. three-necked flask equipped as described for the preparation of ethylenediamine tetraacetic acid was placed 500 cc. of a solution containing 20.0 g. (0.33 mole) of ethylenediamine and 0.40 moles of sodium hydroxide. To this was added, continuously and with stirring, an aqueous solution containing 0.333 mole of the nitrile. The addition was made over a period of 10 hours while the reaction mixture was kept at room temperature. At the end of this time, the mixture was distilled under vacuum until the volume of the remaining liquid was about 500 cc. After further addition of 0.33 moles of sodium hydroxide the reaction mixture was treated as before with one-third mole of glyconitrile and again distilled until the volume had been reduced to 500 cc. The process was repeated twice more in the same manner. The resulting, nearly colorless, reaction mixture was treated with acid as described previously for the isolation of ethylenediamine tetraacetic acid.

The weight of the dried crystals was 41.2 g. representing 42% of the theoretical amount. The nature of the product was established as above with nitrogen analysis and preparation and analysis of the dibarium salt.

Hexamethylenetetramine. The presence of hexamethylenetetramine in the unacidified reaction solution was determined as follows:

A sample of the alkaline solution obtained as a reaction product in the carboxymethylation reaction of ethylenediamine described above and containing 0.0327 mole of the tetrasodium salt, was treated with 0.179 moles of dilute of sulfuric acid and steam-distilled until 400 cc. of distillate had been collected. The distillate was diluted to 1000 cc. and several 25-cc. samples were analyzed for formaldehyde by the peroxide titration method. The results showed that 0.0477 mole of hexamethylenetetramine had been formed per mole of ethylenediamine used in the reaction; assuming all the formaldehyde was formed from hexamethylenetetramine.

Ammonia in the form of ammonium salts was determined by a Van Slyke analysis of the acidified reaction product obtained as in the formaldehyde determination. The results also indicated the formation of 0.048 mole of hexamethylenetetramine per mole of ethylenediamine used.

ACKNOWLEDGMENT

This work was supported by a research fellowship established by the Bersworth Laboratories of Framingham, Massachusetts. The authors also express their appreciation to the reviewer of this paper for valuable suggestions concerning the mechanism of this reaction.

SUMMARY

A detailed procedure is presented for the carboxymethylation of amines, with ethylenediamine as an example. A shorter and more convenient procedure which results in somewhat reduced yields is described. This is a general reaction for the replacement of the hydrogens of aliphatic amines with acetic acid groups. The reaction may be carried out with an alkali cyanide and formaldehyde, or with an alkali hydroxide and glyconitrile.

WORCESTER 3, MASS.

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[Contribution from the Chemical Research Division of Schering Corporation]

α-NAPHTHYL- AND α-TETRALYL-CINNAMIC ACIDS

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Received November 17, 1948

In connection with studies on the reduction of substituted naphthalene compounds with Raney's alloy and aqueous alkali (1), several naphthyl- and tetralylcinnamic acids as well as the corresponding α-naphthyl- and α-tetralyl-propionic acids were required. The Perkin condensation of naphthylacetic acids and nitrobenzaldehydes has been extensively applied for the synthesis of naphthylnitrocinnamic acids (2), the latter substances being intermediates in the Pschorr synthesis of polycyclic hydrocarbons (3). Halogen and alkyl substituted naphthylcinnamic acids (4) have also been secured by this synthesis. However, the preparation and characterization of α(1- and 2-naphthyl)- and α-(1- and 2-*ar*-tetralyl)-cinnamic acids and the *p*-hydroxy derivatives have apparently not been described.

The Perkin condensation of benzaldehyde and *p*-hydroxybenzaldehyde with the anhydrous alkali metal salts of α- and β-naphthaleneacetic acids gave the naphthylcinnamic acids in crude yields of 60–93%. Similarly, the *ar*-tetralylcinnamic acids were obtained in 58–73% yields. The requisite α-*ar*-tetralylacetic acid was secured by Raney alloy reduction of α-naphthaleneacetic acid (1), whereas the β-*ar*-tetralylacetic acid was obtained from 6-acetyltetralin by the morpholine modification of the Willgerodt reaction (5).

In previous publications, it has been shown that cycloalkene- (6) and aryloxyacetic acids (7) may be condensed in fair yield with aromatic aldehydes using equimolecular amounts of potassium acetate or triethylamine. This method has been found applicable to the naphthyl- and *ar*-tetralyl-acetic acids. In the three condensations in which the free arylacetic acids were used, yields comparable to those obtained by the conventional condensation procedure were secured.

Reduction of the α-naphthylcinnamic acids to the α-naphthyl-β-phenylpropionic acids proceeded smoothly in dilute alkali with either Raney's catalyst at 25–30 pounds hydrogen pressure or with sodium amalgam. Somewhat better yields and purer products were obtained with the Raney catalyst reduction. The α-*ar*-tetralyl-β-phenylpropionic acids were secured in practically quantitative yields from the corresponding cinnamic acids by Raney alloy reduction (8).

EXPERIMENTAL

The Perkin condensations were carried out in 3-necked flasks equipped with stirrer, thermometer, and condenser carrying a calcium chloride tube. All melting points are corrected.

α-(α-Naphthyl)cinnamic acid. Method I. A mixture of 93 g. (0.5 mole) of α-naphthaleneacetic acid, 53 g. (0.5 mole) of freshly distilled benzaldehyde, 50 g. (0.5 mole) of anhydrous triethylamine, and 300 cc. of acetic anhydride was heated for 20 hours at 110–115°. After cooling the reaction mixture to 60°, the excess acetic anhydride was decomposed cautiously with water and then the mixture was poured into two liters of 5% hydrochloric acid.

After standing overnight, the supernatant liquid was decanted and the solid cake dissolved in hot sodium carbonate solution. Norit was added and the alkaline solution filtered and acidified; yield 82 g. (60%); m.p. 140–146°. The crude cinnamic acid was dissolved in 500 cc. of 10% sodium hydroxide, the resulting solution saturated with sodium chloride and cooled overnight at 5°. The precipitated sodium salt was filtered, dissolved in water and, after treating with Norit, was filtered. On acidification, the cinnamic acid was obtained as a white crystalline solid, yield 64 g.; m.p. 160–162°. The analytical sample was recrystallized from benzene-petroleum ether, m.p. 165–166°.

Anal. Calc'd for $C_{19}H_{14}O_2$: C, 83.18; H, 5.11.

Found: C, 82.94; H, 5.38.

Method II. The condensation of 44.8 g. (0.2 mole) of anhydrous potassium α-naphthylacetate and 21.2 g. (0.2 mole) of benzaldehyde in 200 cc. of acetic anhydride for eight hours at 105–110° gave 38 g. (69%) of the crude cinnamic acid, m.p. 152–154°. Recrystallized from benzene-petroleum ether, yield 30 g. (55%); m.p. 163–164°.

α-(α-Naphthyl)-β-phenylpropionic acid. This compound was secured from the corresponding cinnamic acid by reduction with Raney's catalyst in 2% sodium hydroxide solution at a pressure of 25–30 lbs. An 80% yield of the propionic acid was obtained, m.p. 136–137°, after recrystallization from benzene-petroleum ether or *n*-hexane.

Anal. Calc'd for $C_{19}H_{16}O_2$: C, 82.57; H, 5.98.

Found: C, 82.40; H, 6.12.

α-(β-Naphthyl)cinnamic acid. This compound was secured from β-naphthaleneacetic acid (9) by method II in 65% yield, m.p. 204–205°. Recrystallized from aqueous alcohol for analysis, m.p. 209.5–210.5°.

Anal. Calc'd for $C_{19}H_{14}O_2$: C, 83.18; H, 5.11.

Found: C, 83.02; H, 5.36.

α-(β-Naphthyl)-β-phenylpropionic acid. A quantitative yield of this compound was obtained by preparing it as described for the corresponding α-compound. Recrystallized from a mixture of ether-petroleum ether, m.p. 148–149°.

Anal. Calc'd for $C_{19}H_{16}O_2$: C, 82.57; H, 5.98.

Found: C, 83.02; H, 5.90.

α-(α-Naphthyl)-p-hydroxycinnamic acid. A mixture of 22.4 g. (0.1 mole) of anhydrous potassium α-naphthaleneacetate, 12.2 g. (0.1 mole) of *p*-hydroxybenzaldehyde and 300 cc. of acetic anhydride was heated for eight hours at 105–110° with stirring. The reaction product, after decomposition with water, was poured into 5% hydrochloric acid and allowed to stand overnight. The crude condensation product was filtered and then dissolved in 300 cc. of 20% sodium hydroxide. The alkaline solution was heated, treated with Norit and filtered. To the filtrate, 100 g. of sodium chloride was added, the mixture heated to boiling, Norit added and the solution then filtered through a heated funnel. On cooling the filtrate, the sodium salt of the cinnamic acid precipitated. It was filtered, dissolved in hot water and treated with Norit. After filtering, the aqueous solution was acidified, yield 26.8 g. (93%); m.p. 170–175°. Recrystallized from acetone-water, yield 18 g. (62%); m.p. 216–216.5°. The product crystallized with a molecule of water.

Anal. Calc'd for $C_{19}H_{14}O_3 \cdot H_2O$: C, 74.02; H, 5.23.

Found: C, 74.04; H, 5.24.

Recrystallized from a mixture of benzene-petroleum ether, the substituted *p*-hydroxycinnamic acid melted at 213–214° after drying *in vacuo* over xylene.

Anal. Calc'd for $C_{19}H_{14}O_3$: C, 78.59; H, 4.86.

Found: C, 78.56; H, 5.05.

The condensation of the free acid, *p*-hydroxybenzaldehyde and triethylamine by method I gave a 66% yield of the crude substituted cinnamic acid, m.p. 180–192°.

α-(α-Naphthyl)-β-(p-hydroxyphenyl)propionic acid. This compound was obtained in 78% yield from the corresponding cinnamic acid (5 g.) by reduction with 200 g. of 5% sodium amalgam in dilute sodium hydroxide solution. The propionic acid melted at 161–162° after recrystallization from ether-petroleum ether.

Anal. Calc'd for $C_{19}H_{16}O_2$: C, 78.05; H, 5.52.
Found: C, 78.23; H, 5.57.

α-(β-Naphthyl)-p-hydroxycinnamic acid. In accordance with method II, a mixture of 61 g. (0.5 mole) of *p*-hydroxybenzaldehyde, 112 g. (0.5 mole) of anhydrous potassium β-naphthylacetate, and 450 cc. of acetic anhydride was heated with stirring for eight hours at 110°. After decomposing the excess acetic anhydride with water, the crude condensation product was purified by solution in sodium carbonate, yield 125 g. (85%); m.p. 211–215°. Recrystallized from aqueous ethanol, yield 105 g.; m.p. 232.5–233.5°. The analytical sample melted at 238–239°.

Anal. Calc'd for $C_{19}H_{14}O_3$: C, 78.59; H, 4.87.
Found: C, 78.62; H, 5.27.

α-(β-Naphthyl)-β-(p-hydroxyphenyl)propionic acid. By reduction with Raney catalyst in alkaline solution at 35–40 pounds, this compound was obtained from the cinnamic acid in quantitative yield, m.p. 198–200°. The analytical sample melted at 206–207° after recrystallization from benzene-petroleum ether.

Anal. Calc'd for $C_{19}H_{16}O_3$: C, 78.05; H, 5.52.
Found: C, 78.15; H, 5.65.

α-(5,6,7,8-Tetrahydro-α-naphthyl)cinnamic acid. Using method II, this compound was obtained from anhydrous potassium α-*ar*-tetralylacetate (1) and benzaldehyde, yield 68%; m.p. 160–162°. Recrystallized from benzene-petroleum ether, m.p. 172–173°.

Anal. Calc'd for $C_{19}H_{18}O_2$: C, 81.99; H, 6.52.
Found: C, 82.28; H, 6.60.

α-(5,6,7,8-Tetrahydro-α-naphthyl)-β-phenylpropionic acid. This compound was obtained by Raney alloy reduction of the corresponding cinnamic acid in 95% yield; m.p. 100–106°. Recrystallized from ligroin (b.p. 65–68°), m.p. 111–112°.

Anal. Calc'd for $C_{19}H_{20}O_2$: C, 81.38; H, 7.19.
Found: C, 81.08; H, 7.07.

α-(5,6,7,8-Tetrahydro-β-naphthyl)cinnamic acid. This acid was secured by method II from anhydrous potassium β-*ar*-tetralylacetate and benzaldehyde, yield 65%; m.p. 160–166°. Recrystallized from aqueous ethanol, m.p. 179–180°.

Anal. Calc'd for $C_{19}H_{18}O_2$: C, 81.99, H, 6.52.
Found: C, 81.93; H, 6.52.

The β-*ar*-tetralylacetic acid was obtained from 6-acetyltetralin (10) by the morpholine modification of the Willgerodt reaction (7). The 6-tetralylthioacetmorpholide was obtained in 94% yield, m.p. 96–104°. Recrystallized from benzene-petroleum ether, m.p. 115–116°.

Anal. Calc'd for $C_{16}H_{21}NOS$: N, 5.09. Found: N, 5.40.

Hydrolysis with alcoholic alkali gave an 84% yield of the crude β-*ar*-tetralylacetic acid. Recrystallized from benzene, m.p. 98.5–99.5°, literature m.p. 97.2–97.5° (10).

α-(5,6,7,8-Tetrahydro-β-naphthyl)-β-phenylpropionic acid. This compound was obtained from the corresponding cinnamic acid by reduction with Raney's alloy and aqueous alkali, yield 90%; m.p. 88–89° after recrystallization from ligroin (b.p. 65–68°).

Anal. Calc'd for $C_{19}H_{20}O_2$: C, 81.38; H, 7.19.
Found: C, 81.20; H, 6.82.

α-(5,6,7,8-Tetrahydro-α-naphthyl)-p-hydroxycinnamic acid. A mixture of 22.8 g. (0.1 mole) of anhydrous potassium *ar*-tetrahydro-α-naphthylacetate and 12.2 g. (0.1 mole) of *p*-hydroxybenzaldehyde in 300 cc. acetic anhydride was heated for eight hours at 110–115° with stirring. The crude α-(5,6,7,8-tetrahydro-α-naphthyl)-*p*-hydroxycinnamic acid, after recrystallization from benzene-petroleum ether, melted at 221–221.5°; yield 17 g. (58%).

Anal. Calc'd for $C_{19}H_{18}O_3$: C, 77.53; H, 6.17.
Found: C, 77.72; H, 6.35.

α-(5,6,7,8-Tetrahydro-α-naphthyl)-β-(p-hydroxyphenyl)propionic acid. This acid was

obtained from the corresponding cinnamic acid either by reduction with Raney's catalyst in alkaline solution at 25 lbs. pressure or by treating with Raney's alloy and aqueous alkali. Recrystallized from benzene, m.p. 175–176°.

Anal. Calc'd for $C_{19}H_{20}O_3$: C, 76.99; H, 6.87.

Found: C, 77.06; H, 7.13.

α-(5,6,7,8-Tetrahydro-β-naphthyl)-p-hydroxycinnamic acid. Using method I, this compound was obtained from β-*ar*-tetralylacetic acid and *p*-hydroxybenzaldehyde in 73% yield, m.p. 201–202° after recrystallization from aqueous ethanol.

Anal. Calc'd for $C_{19}H_{18}O_3$: C, 77.53; H, 6.17.

Found: C, 77.66; H, 6.20.

α-(5,6,7,8-Tetrahydro-β-naphthyl)-β-(p-hydroxyphenyl)propionic acid. This compound was obtained from the corresponding cinnamic acid by Raney alloy reduction, yield 95%; m.p. 205–206° after recrystallization from aqueous ethanol.

Anal. Calc'd for $C_{19}H_{20}O_3$: C, 76.99; H, 6.87.

Found: C, 76.81; H, 6.80.

SUMMARY

The Perkin synthesis of naphthyl- and *ar*-tetralyl-cinnamic acids and the *p*-hydroxy derivatives is described. The naphthylcinnamic acids were reduced to the corresponding propionic acids by sodium amalgam or Raney's catalyst, whereas the *ar*-tetralylcinnamic acids were reduced with Raney's alloy in aqueous alkali.

BLOOMFIELD, NEW JERSEY

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[Contribution from the Chemical Research Division of Schering Corporation]

REDUCTIONS WITH NICKEL-ALUMINUM ALLOY AND AQUEOUS ALKALI. PART VI. NAPHTHALENE AND ITS SUBSTITUTION PRODUCTS[1]

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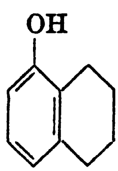
Received November 22, 1948

In a previous publication (1) from these laboratories, the displacement of sulfonic acid groups by the action of a nickel-aluminum alloy in aqueous alkali was reported. In the case of naphthalene sulfonic acids, simultaneous reduction to tetrahydronaphthalenes accompanied hydrogenolysis of the sulfonic acid groups. This paper describes the results of our studies on the application of the Raney alloy reduction procedure to a variety of mono- and di-substituted naphthalene compounds.

The hydrogenation of naphthalene and naphthalene derivatives to the corresponding tetrahydro and decahydro compounds has been the subject of many investigations. The classical studies of Bamberger (2) on the reduction of naphthalene derivatives by means of sodium and alcohols established the marked difference in reactivity of the substituted and unsubstituted rings of the naphthols. While α-naphthol reduces almost exclusively in the unsubstituted ring to give the phenolic, *ar*-α-tetralol (I), β-naphthol reduces to the alcohol, *ac*-β-tetralol (II).



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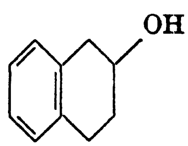

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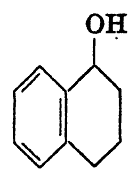

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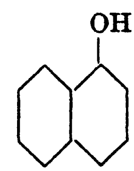


IV

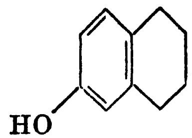
The course of the catalytic hydrogenation of the naphthols depends primarily upon the nature of the catalyst. With α-naphthol, there may be obtained in addition to I, the alcohols (III) and (IV), as well as tetralin, the latter resulting from the hydrogenolysis of (III) (3a). For example, with Raney nickel catalyst, α-naphthol gives (I) and (III) in a ratio of 5:3, whereas over copper chromite the ratio is 1:2 respectively. On the other hand, β-naphthol, over either catalyst, has been reported to hydrogenate almost exclusively in the oxygenated ring to the alcohol (II).

However, Stork (3d) has shown recently that β-naphthol[2] with "neutral" Raney nickel catalyst at 85–100° and at an initial pressure of about 3,500 lbs. is hydrogenated to the *ar*-β-tetralol (V) in 66% yield. Under identical condi-

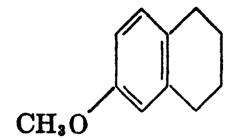
[1] Presented in abstract before the Division of Organic Chemistry at the New York Meeting of the American Chemical Society on September 15, 1947.

[2] In studying the preparation of β-tetralone by the catalytic hydrogenation of β-naphthol with Raney nickel catalyst, Stock and Foreman (3c) isolated a tetralol fraction which consisted predominately of the phenolic *ar*-β-tetralol.

tions except for the presence of a small quantity of base, β-naphthol reduces preferentially in the substituted ring to the alcohol (II). β-Naphthyl methyl ether gave 60% of 6-methoxytetralin (VI) with "neutral" Raney nickel catalyst.



V



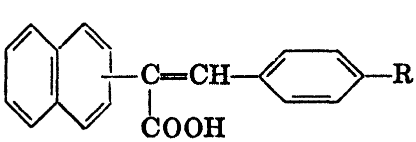
VI

In general, catalytic hydrogenation of naphthalene or substituted naphthalenes to the decahydro derivatives is relatively simple; whereas the selective hydrogenation of one of the benzenoid nuclei is often difficult, particularly for substituted naphthalenes when hydrogenation of either the substituted or unsubstituted ring is desired. Although chemical reduction (sodium and alcohols) gives, almost without exception, the tetrahydro derivatives, preferential reduction of either ring is also not always feasible. Hydrogenolysis occasionally accompanies catalytic and chemical reduction, this side reaction being more frequently encountered in the catalytic procedures.

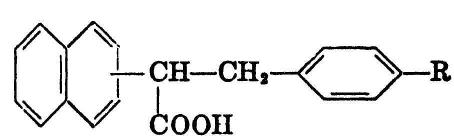
The use of an alkali solution together with Raney's alloy for effecting the reduction of organic compounds has been without effect on the hydrogenation of benzene or substituted benzene compounds. However, naphthalene and its derivatives reduce readily to the corresponding tetrahydro compounds by the alloy method; the hydrogenation of several compounds proceeds smoothly even at room temperature.

Naphthalene reduced in good yield to tetralin and many of the monosubstituted naphthalenes reduced exclusively in the non-substituted ring. For example, α-naphthol, α-nitronaphthalene, β-naphthoic acid, α-naphthaleneacetic acid and β-(2-naphthoyl)propionic acid yielded the corresponding *ar*-tetrahydro derivatives. With β-naphthol and α-naphthoic acid, reduction occurs in both the substituted and unsubstituted rings. In the former case, approximately 55–60% of *ar*-β-tetralol was formed. This result is somewhat unexpected in view of Stork's findings (3d). β-Naphthaleneacetic acid reduced in the substituted ring and an 85% yield of recrystallized *ac*-β-tetralylacetic acid was obtained. In the latter case there was no evidence that any reduction in the unsubstituted ring occurred.

Several α-(1- and 2-naphthyl)cinnamic and β-(1- and 2-naphthyl)-β-phenylpropionic acids of the following formulas (VII–XIV) reduced in either the sub-



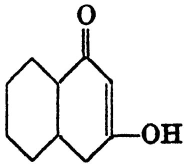
VII α-$C_{10}H_7$-; R, H
IX β-$C_{10}H_7$-; R, H
XI α-$C_{10}H_7$-; R, OH
XIII β-$C_{10}H_7$-; R, OH



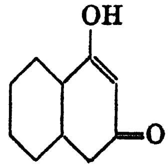
VIII α-$C_{10}H_7$-; R, H
X β-$C_{10}H_7$-; R, H
XII α-$C_{10}H_7$-; R, OH
XIV β-$C_{10}H_7$-; R, OH

stituted or unsubstituted ring. Compounds VII and VIII gave approximately equal amounts of the *ar*- and *ac*-compounds, whereas IX and X gave a predominant amount of the *ar*-compound and only about 15% of the *ac*-compound. For XI–XIV inclusive, only one reduction product was isolated and identified, the *alpha* compounds, XI and XII, reducing in the substituted ring, whereas the *beta* compounds, XIII and XIV, reduced in the unsubstituted ring. The reduction products of compounds VII–XIV were identified by analysis and mixed melting point with authentic samples of α-(tetralyl)-β-phenylpropionic acid (4).

Several disubstituted naphthalenes wherein the substituents are on either one ring or on both rings have also been studied. The former are reduced in the unsubstituted ring, 3-hydroxy-β-naphthoic acid and 1-hydroxy-β-naphthoic acid yielding the corresponding *ar*-β-tetrahydro derivatives in good yield. However, 1,3-dihydroxynaphthalene gave an unusual reduction product, which analyzed for a dihydroxyhexahydronaphthalene of probable formula XV or XVI. In a patent (5), the catalytic reduction of 1,3-dihydroxynaphthalene is stated to yield a hexahydro derivative. However, neither the procedure for the catalytic reduction nor physical data for the compound is given.



XV



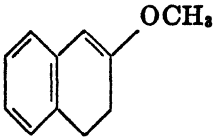
XVI

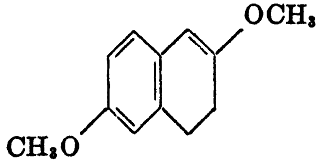
The disubstituted naphthalenes having one substituent on each ring gave in the case of 2,7-dihydroxy- and 1,8-dicarboxy-naphthalenes the expected 2,7-dihydroxy- and 1,8-dicarboxy-tetralins respectively. However, 1,5-dinitronaphthalene yielded *ar*-tetrahydro-α-naphthylamine, a nitro or an amino group being hydrogenolyzed in the course of the reaction.

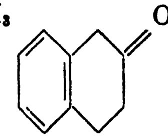
A most unexpected result was obtained with 1,5-dihydroxy- and 1,6-dihydroxy-naphthalenes. Instead of the expected 1,5- and 1,6-dihydroxytetralins, there was obtained 5-hydroxy- and 6-hydroxy-α-tetralones respectively. It is difficult to reconcile these results with the known susceptibility of carbonyl groups to the Raney alloy (6) and Raney catalyst (7) reduction methods. It is apparent, especially in the case of 1,6-dihydroxynaphthalene, that the tetralone is the direct product of the reduction, further reduction of the carbonyl group being rendered difficult by the fact that it is essentially an acid carbonyl (8). The 6-hydroxy-α-tetralone can be recovered quantitatively after treatment with Raney's alloy and aqueous alkali. Although only a poor yield of 5-hydroxy-α-tetralone was obtained as the 5-methoxy compound, the 6-hydroxy-α-tetralone was secured in 70% yields on ten-gram reductions of 1,6-dihydroxynaphthalene. This procedure appears considerably simpler than those published for securing 6-methoxy-α-tetralone (3d, 9).

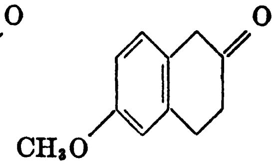
In the course of the reduction of the naphthalene nucleus, other groups susceptible to reduction by the alloy method such as the nitro groups, keto groups and double bonds are simultaneously reduced.

Hydrogenolysis was also encountered in the case of β-naphthyl methyl ether, the principal product of the reaction being tetralin. Approximately 30–35% of the β-naphthyl methyl ether was recovered unchanged. With sodium and alcohol, β-naphthyl methyl ether and 2,6-dimethoxynaphthalene reduce to the dihydro derivatives XVII and XVIII respectively (10). On hydrolysis, XVII


XVII


XVIII


XIX


XX

and XVIII yield the ketones XIX and XX. With Raney alloy and aqueous alkali, 1,6-dimethoxynaphthalene yielded several products, tetralin being the only one definitely identified.

EXPERIMENTAL

The reductions were carried out as previously described (1). It was necessary to modify the procedure for several compounds and the reduction for these compounds is described in detail. Except in those cases where the amounts of starting material are given, 10 g. of substance in 300 cc. of 10% sodium hydroxide solution was reduced with 20 g. of Raney's alloy. The yields are calculated to the purified reduction product. Alkali-insoluble compounds were reduced in a 2,000-cc. flask equipped with an adapter and efficient reflux condenser. All melting points have been corrected.

1. *Naphthalene* was reduced using 50 cc. of ethyl alcohol as solvent. A 74% yield of *tetralin* was obtained, b.p. 203–205°. With *phthalic anhydride*, the *o-tetrahydronaphthoylbenzoic acid* was obtained, m.p. 155–156° in agreement with the literature (11).

2. *α-Naphthol* gave an 85% yield of *ar-tetrahydro-α-naphthol*. Recrystallized from petroleum ether, m.p. 70–71°, literature 68.5–70° (12). Addition product with 1,3,5-trinitrobenzene was obtained as golden yellow needles, m.p. 108–110°, literature 106–107° (13).

3. To 25 g. of *β-naphthol* dissolved in 600 cc. of 10% sodium hydroxide, there was added 40 g. of Raney's alloy. The reduction product was extracted with chloroform from the acidified solution, the chloroform extract washed, dried and evaporated; yield 17.5 g., m.p. 56–58°. Recrystallized from petroleum ether, it had m.p. 60–61°; literature 59–60° (3b). The *ac-β*-tetralol was lost by steam distillation during the reduction.

4. *Reduction of 1,3-dihydroxynaphthalene.* Five grams of 1,3-dihydroxynaphthalene was reduced in 250 cc. of 10% sodium hydroxide solution with 20 g. of Raney's alloy. The reduction was carried out in an atmosphere of nitrogen. The reduction product was worked up and after two recrystallizations from *n*-hexane it melted at 108–110°.

Anal. Calc'd for $C_{10}H_{14}O_2$: C, 72.25; H, 8.48.

Found: C, 72.19; H, 8.35.

5. *1,5-Dihydroxynaphthalene.* To one liter of 5% sodium hydroxide in a two-liter, three-necked flask carrying a condenser and gas delivery tube, there was added 10 g. of 1,5-dihydroxynaphthalene. After replacing the air with nitrogen, the reaction mixture was heated to 40–50° and 25 g. of Raney's alloy added in small portions over a period of 1½–2 hours. The reaction temperature rose to 65–70° and after one hour at this temperature the reaction mixture was filtered into a mixture of ice and hydrochloric acid. The acidified solution was extracted with ether and after removing the solvent in a nitrogen atmosphere, 7.4 g. of a brown crystalline mass was obtained. The crude reduction product was methylated with dimethyl sulfate and the product separated into 1,5-dimethoxynaphthalene

(m.p. 182–184°) and 5-methoxy-α-tetralone [yield 2.1 g., m.p. 87–88°; literature m.p. 89–89.5° (14)] by recrystallization from petroleum-ether. The *semicarbazone* of 5-methoxy-α-tetralone melted at 249–250° in agreement with the literature (14).

6. Technical *1,6-dihydroxynaphthalene* was recrystallized from benzene, m.p. 137–138°. Ten grams was reduced as described for the 1,5-dihydroxy compound. The reaction mixture was filtered directly into a mixture of ice and concentrated hydrochloric acid, stirred to completely dissolve the aluminum salts, and then extracted with ether. The ether residue yielded 7 g. of a tan product, m.p. 137–141°. Recrystallized from water, 6.1 g. of *6-hydroxy-α-tetralone* was obtained, m.p. 150–152°, literature m.p. 150° (15).

Anal. Calc'd for $C_{10}H_{10}O_2$: C, 74.04; H, 6.22.
Found: C, 73.64; H, 6.22; 5.87.

The *semicarbazone* was prepared in the usual manner and recrystallized from alcohol, m.p. 216.5–217.5°.

Anal. Calc'd for $C_{11}H_{13}N_3O_2$: C, 60.25; H, 5.98; N. 19.17.
Found: C, 59.98; H, 6.23; N, 19.24.

The *6-acetoxy-α-tetralone* was prepared as described (16) and after recrystallization from aqueous methyl alcohol melted at 60–61°, literature 61–62°.

7. *2,7-Dihydroxynaphthalene* gave an 86% yield of the *tetrahydro* derivative, m.p. 123–132°. Recrystallized from water, m.p. 146–147°.

Anal. Calc'd for $C_{10}H_{12}O_2$: C, 73.12; H, 7.32.
Found: 73.19; H, 7.25.

8. *α-Naphthoic acid* gave a mixture of the *ar-* and *ac-tetrahydro-α-naphthoic acid*. From 20 g. of α-naphthoic acid, 16 g. of the mixed acids was obtained which melted at 70–86°. This product was converted to the ethyl esters, yield 16 g.; b.p. 102–103°/1 mm.

Anal. Calc'd for $C_{13}H_{16}O_2$: C, 76.42; H, 7.91.
Found: C, 76.55; H, 8.14.

The mixed esters were saponified but attempts to separate the two isomeric acids by crystallization or by formation of the amides were fruitless.

9. *β-Naphthoic acid* yielded 85% of *ar-tetrahydro-β-naphthoic acid* which melted at 152.5–153.5° after two recrystallizations from dilute methyl alcohol. Previously reported m.p. 143° (17), 153° (18). This compound has been secured by the Friedel-Crafts reaction between tetralin and acetyl chloride with the subsequent oxidation of the 2-acetyl derivative (17). It has also been obtained by catalytic reduction with Raney nickel (3d).

Anal. Calc'd for $C_{11}H_{12}O_2$: C, 74.96; H, 6.82.
Found: C, 74.65; H, 7.16.

10. To 50 g. of *α-naphthalenaecetic acid* dissolved in 1,000 cc. of 10% sodium hydroxide, was added gradually 75 g. of Raney's alloy. The reduction product was isolated in the usual manner and after recrystallization from benzene-petroleum ether 36 g. of *ar-α-tetrahydronaphthaleneacetic acid*[3] melting at 131–132° was obtained; mixed m.p. with α-naphthaleneacetic acid 115–118°.

Anal. Calc'd for $C_{12}H_{14}O_2$: C, 75.75; H, 7.42.
Found: C, 75.79; H, 7.64.

The reduction product readily underwent a Perkin condensation with *p*-hydroxybenzaldehyde (4). Oxidation with alkaline permanganate gave hemimellitic acid, m.p. 188–190° after recrystallization from dilute aqueous hydrochloric acid; literature m.p. 190° (dec.) (19). The anhydride melted at 194–196°, literature 196° (19).

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[3] *Ac-α*-tetralylacetic acid has been obtained by the Reformatsky reaction from α-tetralone and ethyl bromoacetate, followed by dehydration, saponification and reduction. It is reported as a viscous oil [Schroeter, *Ber.*, **58**, 713 (1925)] and a solid, m.p. 35–36° [v. Braun, Gruber, and Kirschbaum, *Ber.*, **55**, 3664 (1922)]. In an attempt to obtain β-(α-naphthyl)-ethyl alcohol, de Pommereau [*Compt. rend.*, **175**, 105 (1922)] reduced ethyl α-naphthylacetate with sodium and alcohol. Instead of the expected substituted ethyl alcohol, a tetralylacetic acid was obtained melting at 131°. Although no proof of structure for this acid was given, its melting point is in agreement with that of our *ar-α*-tetralylacetic acid.

11. Twenty grams of *β-naphthaleneacetic acid* was reduced in 500 cc. of 10% sodium hydroxide with 40 g. of Raney's alloy. The crude *tetrahydro acid* was recrystallized from petroleum ether, yield 17 g.; m.p. 53.5–55°. Recrystallized for analysis, m.p. 54–55°.

Anal. Calc'd for $C_{12}H_{14}O_2$: C, 75.75; H, 7.42.

Found: C, 75.94; H, 7.56.

The reduction occurred in the substituted ring to give the *ac-β*-tetralylacetic acid since the *ar-β*-tetralylacetic acid prepared by an unequivocal synthesis melted at 97–98° (4).

12. *Naphthalic anhydride* was reduced to *tetralin-1,8-dicarboxylic acid*, yield 86%; m.p. 185–186° after recrystallization from aqueous alcohol, literature 185° (20).

Anal. Calc'd for $C_{12}H_{12}O_4$: C, 65.42; H, 5.50.

Found: C, 65.40; H, 6.02.

13. *1-Hydroxy-β-naphthoic acid* was prepared as follows (21): 14.4 g. of α-naphthol was added gradually to 2.5 g. of powdered sodium in 150 cc. of dry toluene. The mixture was heated to boiling and a stream of carbon dioxide bubbled in for 1½ hours. After cooling, the unreacted sodium was destroyed with 50 cc. of ethyl alcohol and the solvents removed by steam distillation. The steam-distillation residue was cooled and carbon dioxide was bubbled into the solution. The unreacted α-naphthol was filtered off and the filtrate acidified with sulfuric acid. The 1-hydroxy-β-naphthoic acid was filtered and purified through the sodium salt, yield, 8.6 g.; m.p. 186–188°; literature 185–186°; 186–188° (22).

Reduction of 5 g. of this acid gave 4.1 g. of the *1-hydroxy-ar-tetrahydro-β-naphthoic acid* which melted after recrystallization from dilute alcohol at 156–158°. A deep reddish-brown dye was obtained with nitrodiazobenzene.

Anal. Calc'd for $C_{11}H_{12}O_3$: C, 68.71; H, 6.30.

Found: C, 69.09; H, 6.19.

14. *3-Hydroxy-β-naphthoic acid* gave *3-hydroxy-ar-tetrahydro-β-naphthoic acid* in 85% yield. Recrystallized from dilute methyl alcohol, m.p. 179–180°, literature 182° (23).

Anal. Calc'd for $C_{11}H_{12}O_3$: C, 68.71; H, 6.30.

Found: C, 69.05; H, 6.67.

The *acetate* was prepared in the usual manner and recrystallized from benzene-petroleum ether, m.p. 140–142°.

Anal. Calc'd for $C_{13}H_{14}O_4$: C, 66.70; H, 6.03.

Found: C, 66.64; H, 6.35.

15. *Reduction of β-(2-naphthoyl)propionic acid.* Ten grams of the acid was dissolved in 1,000 cc. of 10% sodium hydroxide and the reduction carried out in the usual manner with 50 g. of Raney's alloy. The reaction mixture was filtered from the nickel, acidified, and extracted with ether. The ether residue was distilled, yield 6 g.; b.p. 184–190°/3 mm. Recrystallized from petroleum ether, the *γ-(5,6,7,8-tetrahydro-β-naphthyl)butyric acid* melted at 49–50° in agreement with the literature (24).

16. *α-Nitronaphthalene* gave *ar-tetrahydro-α-naphthylamine* which was isolated by steam distillation, yield 65%; b.p. 261–263°. This substance on diazotization coupled readily with β-naphthol. The *acetyl* derivative, after recrystallization from water, melted at 156–157°; literature 158° (25). The *ar-tetrahydro-α-naphthylamine hydrochloride* was prepared in the usual manner and melted at 259–261°.

Anal. Calc'd for $C_{10}H_{14}ClN$: Cl, 19.32. Found: Cl, 19.49.

17. *Reduction of 1,5-dinitronaphthalene.* To 500 cc. of 10% sodium hydroxide solution, 10 g. of 1,5-dinitronaphthalene and 50 cc. of ethyl alcohol were added. After heating the reaction mixture to approximately 40°, 40 g. of Raney's alloy was added in small portions in a course of 2 hours. The reaction mixture was heated for an additional two hours on the steam-bath and then steam distilled. The steam-distillate was extracted with ether, the ether dried and evaporated. The residue was taken up in anhydrous benzene and gaseous hydrochloric acid passed in until precipitation of the amine hydrochloride was complete. After recrystallizing from absolute alcohol and ether, 4.4 g. of the pure hydrochloride was obtained, m.p. 257.5–258°. Mixed melting point with 5,6,7,8-tetrahydro-α-naphthylamine hydrochloride, 258–259°.

18. *Reduction of β-naphthyl methyl ether.* To 500 cc. of 10% sodium hydroxide in a 2-l.

flask equipped with adapter and condenser, there was added 20 g. β-naphthyl methyl ether, 50 cc. of ethyl alcohol and 50 cc. of toluene. After heating the mixture to about 50°, 30 g. of Raney's alloy was gradually added over a period of 1½–2 hours. The reaction mixture was filtered, diluted with 500 cc. of water, extracted with chloroform, dried and fractionally distilled. Fraction I, yield 2.5 g.; b.p. 85–100°/11 mm.; fraction II, yield 10 g.; b.p. 135°/10 mm., m.p. 69–71°. Fraction I was redistilled, b.p. 86–88°/20 mm.; yield 1.7 g. This was identified as *tetralin*, m.p. and mixed m.p. of *o*-tetrahydronaphthoylbenzoic acid, 156–158°. Fraction II was identified as starting material, m.p. and mixed m.p. 72.5–73°; *picrate*, m.p. and mixed m.p. 116–117°.

19. *Reduction of α-(α-naphthyl)cinnamic acid (4).* Ten grams of this acid was reduced in the usual manner and the acidified solution extracted with ether. The combined ether extracts after drying were evaporated and the resulting oily residue partially crystallized on standing overnight. The crystalline product was freed of oil by filtration and washing with petroleum ether. Yield 5 g.; m.p. 132–134°. Recrystallized from ligroin (b.p. 75–90°) for analysis, m.p. 136–137°.

Anal. Calc'd for $C_{19}H_{20}O_2$: C, 81.38; H, 7.20.
Found: C, 81.48; H, 7.13.

After removing the petroleum ether, the oily product was esterified with ethanol and sulfuric acid and the crude ester distilled and saponified; yield 2.6 g.; m.p. 109–110° after recrystallization from *n*-hexane. Mixed m.p. with α-(5,6,7,8,tetrahydro-α-naphthyl)-β-phenylpropionic acid (4) 109–111°. The product m.p. 136–137° is therefore the isomeric α-(1,2,3,4-tetrahydro-α-naphthyl)-β-phenylpropionic acid.

20. *α-(α-naphthyl)-β-phenylpropionic acid* was reduced as described for the corresponding cinnamic acid. From the oily residue obtained from the ether extracts 5 g. of *α-(1,2,3,4-tetrahydro-α-naphthyl)-β-phenylpropionic acid* was obtained; m.p. 136–137° after recrystallization from ligroin (b.p. 75–90°). Mixed melting point with the product from experiment 19, 136–137°.

Anal. Calc'd for $C_{19}H_{20}O_2$: C, 81.38; H, 7.20.
Found: C, 81.18; H, 7.03.

The oily residue obtained from the evaporation of the recrystallization solvent was seeded with pure α-(5,6,7,8-tetrahydro-α-naphthyl)-β-phenylpropionic acid. After standing for several days a small amount of crystalline material was obtained which melted at 107–109° after recrystallization from *n*-hexane. Mixed m.p. 108–109°.

21. *Reduction of α-(β-naphthyl)cinnamic acid.* To 20 g. of the cinnamic acid in 600 cc. of 10% sodium hydroxide there was added, in the course of 3 hours, 50 g. of Raney's alloy. The crude reduction product was oily and after standing overnight at 0° it partially solidified. The crystalline product was filtered off, yield 2 g. Recrystallized from ligroin (b.p. 65–68°), yield 1.5 g.; m.p. 132–134°. Recrystallized for analysis, m.p. 137–138°.

Anal. Calc'd for $C_{19}H_{20}O_2$: C, 81.38; H, 7.19.
Found: C, 81.46; H, 7.46.

The residual oily product was esterified in the usual manner and the ester distilled, yield 12 g.; b.p. 187–190°/1 mm.; n_D^{25} 1.5600.

Anal. Calc'd for $C_{21}H_{24}O_2$: C, 81.77; H, 7.85.
Found: C, 82.02; H, 7.83.

Two grams of the ester was saponified and the product recrystallized from petroleum ether. Yield 1.5 g., m.p. 87–88°. Recrystallized for analysis, m.p. 90–91°.

Anal. Calc'd for $C_{19}H_{20}O_2$: C, 81.38; H, 7.19.
Found: C, 81.20; H, 6.82.

The latter product was identified by melting point and mixed melting point of 89–90° as *α-(5,6,7,8-tetrahydro-β-naphthyl)-β-phenylpropionic acid* (4). The product m.p. 137–138° is undoubtedly the isomeric *α-(1,2,3,4-tetrahydro-β-naphthyl)-β-phenylpropionic acid.*

22. *Reduction of α-(β-naphthyl)-β-phenylpropionic acid.* This acid was reduced as described for the corresponding α-naphthyl compound, experiment 20. After extracting the acidified solution with ether, the ether extracts were dried and evaporated to dryness. The residue on standing partially crystallized and the crystals were filtered off and washed

with cold petroleum ether. The crystalline product amounted to 2.4 g. and melted after recrystallization from ligroin (b.p. 65–68°) at 135–136°. Mixed melting point with product obtained under experiment 21 showed no depression.

The residual oily product was esterified, the ester distilled and then saponified as described under experiment 21. The yield of *α-(5,6,7,8-tetrahydro-β-naphthyl)-β-phenylpropionic acid* was 6 g.; m.p. 87–88°. Mixed m.p. 87–89°.

23. *Reduction of α-(α-naphthyl)-p-hydroxycinnamic acid.* Five grams of the cinnamic acid (4) was reduced with 20 g. Raney's alloy in 400 cc. of 10% sodium hydroxide; yield 5 g.; m.p. 183–189°. Recrystallization from benzene yielded long, fine, white needles, m.p. 198–199°.

Anal. Calc'd for $C_{19}H_{20}O_3$: C, 76.99; H, 6.87.
Found: C, 76.88; H, 7.08.

This product is the *α-(1,2,3,4-tetrahydro-α-naphthyl)-β-(p-hydroxyphenyl)propionic acid* since the isomeric α-(5,6,7,8-tetrahydro-α-naphthyl)-β-(p-hydroxyphenyl)propionic acid melts at 175–176° (4).

24. *The reduction* of α-(α-naphthyl)-β-(p-hydroxyphenyl)propionic acid (4) gave an 85% yield of *α-(1,2,3,4-tetrahydro-α-naphthyl)-β-(p-hydroxyphenyl)propionic acid*, m.p. 197.5–198°; mixed m.p. with product of experiment 23, 198–199°. The residue from the recrystallization melted at about 165° and attempts to isolate a compound of definite melting point were unsuccessful.

25. *Reduction of α-(β-naphthyl)-p-hydroxycinnamic acid.* To a solution of 20 g. of the acid (4) in 750 cc. of 10% sodium hydroxide there was added 45 g. of Raney's alloy in the course of 3–3½ hours. The reduction product was isolated in the usual manner, yield 20 g.; m.p. 186–188°. Recrystallized from aqueous alcohol or benzene-petroleum ether, m.p. 199–200°.

Anal. Calc'd for $C_{19}H_{20}O_3$: C, 76.98; H, 6.81.
Found: C, 76.81; H, 6.50.

The reduction product was *α-(5,6,7,8-tetrahydro-β-naphthyl)-β-(p-hydroxyphenyl)propionic acid* (4), mixed m.p. 200–201°.

26. *Reduction of α-(β-naphthyl)-β-(p-hydroxyphenyl)propionic acid.* To 5 g. of the propionic acid in 200 cc. of 10% sodium hydroxide, was added in the course of 1½ hours 15 g. of Raney's alloy. The crude reduction product was obtained in quantitative yield, m.p. 182–188°. Recrystallized from benzene-petroleum ether, yield 4.5 g.; m.p. 199–201°. Mixed m.p. with product of experiment 25, 199–200°.

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SUMMARY

Naphthalene and its substitution products are reduced readily to the tetrahydro derivatives with Raney's alloy and aqueous alkali. In general, mono- and di-substituted naphthalenes give the corresponding tetralins in good yield. Unusual reduction products were obtained in the case of 1,5- and 1,6-dihydroxy naphthalenes, 5-hydroxy- and 6-hydroxy-α-tetralones being obtained respectively.

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[Contribution from the Chemistry Laboratory of The Ohio State University]

THE ORIENTATION OF BENZO[c]PHENANTHRENE[1]

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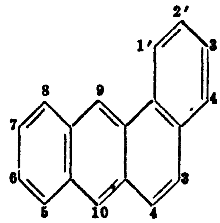
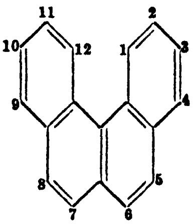
In surveying the information concerning the carcinogenic activity of the monomethyl derivatives of polycyclic aromatic hydrocarbons it appears that when a methyl group is substituted at a position of high chemical activity the resulting derivative is an active carcinogenic agent. Of the twelve monomethyl-1,2-benzanthracenes all of which have been synthesized (1) the most active are the 5-, 9-, and 10-derivatives (2). When the parent hydrocarbon, 1,2-benzanthracene (I), is reacted with various reagents, the substituent enters the 10-position preferentially (3).



I



II

The work herein reported was undertaken to find out which position in benzo[c]phenanthrene[3] (II), was most active chemically. We have prepared a quantity of II and subjected it successfully to nitration, bromination, and acetylation. In each case the substituent entered position 5 preferentially.[4] Although the testing of all of the monomethyl derivatives of II has not been completed,[5] the 5-methyl compound is the most potent carcinogen on the basis of available data.

In view of the present state of knowledge concerning the relative carcinogenic activity of the monomethyl derivatives of I, II, and chrysene[6] it appears unde-

[1] The material herein presented is taken from the Ph.D thesis of Alvin I. Kosak, The Ohio State University, June, 1948.

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[4] It is of interest to note that the calculations of Pullman, *Ann. chim.*, **12**, 5 (1947) and Berthier, Coulson, Greenwood, and Pullman, *Compt. rend.*, **226**, 1906 (1948), place the position of maximum electron density at carbon 5.

[5] Data on the carcinogenic activity of 1-methylbenzo[c]phenanthrene, recently synthesized by Newman and Wheatley, *J. Am. Chem. Soc.*, **70**, 1913 (1948), has not yet been reported.

[6] Because of the general lack of carcinogenic activity in the chrysene series, comparisons are probably of little value. However, it is noteworthy that 5- and 6-methylchrysene have been reported to have cancer producing activity, Dunlap and Warren, *Cancer Research*, **3**, 606 (1943); *Cf.* (2) (a), pg. 87. Newman and Cathcart, *J. Org. Chem.*, **5**, 618 (1940), proved that chrysene is substituted in the 6-position.

sirable at this time to do more than point out the interesting fact that the substitution of a methyl group at (or adjacent to) a position of high chemical reactivity produces an active carcinogenic agent.

The required benzo[*c*]phenanthrene was prepared essentially by Hewett's method (4); the following observations seem worthy of comment. 1-Bromo-2-methylnaphthalene (5) is more completely and easily converted to 1-bromo-2-bromomethylnaphthalene by N-bromosuccinimide (6) than by the high temperature bromination procedure recommended (5). We were unable to attain the yield of α-(1-bromo-2-naphthyl)-β-phenylacrylic acid in the condensation of benzaldehyde with sodium 1-bromo-2-naphthylacetate reported by Hewett (4). However, we obtained the desired acid in 50% yield by a procedure patterned after that of Hauser and Patterson (7). We were able to obtain a good yield of α-(1-bromo-2-naphthyl)-β-phenylacrylonitrile by condensation of benzaldehyde with 1-bromo-2-naphthylacetonitrile but, in agreement with Hewett (4), hydrolysis to the corresponding acid could not be effected. The decarboxylation of 6-benzo[*c*]phenanthrenecarboxylic acid was accomplished in 79% yield by refluxing in quinoline with copper bronze (4) or better (88%) by heating with a copper chromite catalyst, 37KAF, (8) at 300°.

Bromination of II yielded a complex mixture of products from which a monobromo compound was isolated in 59% yield as its complex with 2,4,7-trinitrofluorenone, hereinafter designated TNF (9). Other polybromo compounds were also produced but were not identified. The pure bromo compound obtained from the TNF complex by chromatography melted at 76.6–77.6° and was converted into a cyanide by heating with cuprous cyanide and pyridine (10). This cyanide had the same melting point, 129°, as that reported by Hewett (11), and on hydrolysis was converted into the known 5-benzo[c]phenanthrenecarboxylic acid (12). Attempted bromination of II with N-bromosuccinimide in the presence of benzoyl peroxide or of aluminum chloride failed (12a), the hydrocarbon being recovered almost completely in the first case and an unpromising mixture being obtained in the second.

Nitration of II with mixed acid in acetic acid yielded a mononitro (54% yield) and two dinitro derivatives. The mononitro compound was proved to be the 5-nitro derivative by reduction to the amino compound and comparison of its TNF complex with that formed from 5-aminobenzo[*c*]phenanthrene prepared by a Curtius degradation of authentic 5-benzo[*c*]phenanthrenecarboxylic acid. Attempts to reduce 5-nitrobenzo[*c*]phenanthrene by several standard methods failed. The reduction was accomplished by heating with titanous chloride and hydrochloric acid (13). No attempts were made to determine the structure of the dinitro compounds.

Acetylation of II with acetic anhydride and aluminum chloride in chlorobenzene afforded an acetyl derivative which was proved to be 5-benzo[*c*]phenanthryl methyl ketone by hypochlorite oxidation to 5-benzo[*c*]phenanthrenecarboxylic acid. No pure acetyl derivative could be isolated when acetyl chloride was used.

The various interconversions of the 5-substituted benzo[c]phenanthrenes are shown in the chart.

$$
\begin{tikzcd}
 & C_{18}H_{12} \arrow[dl] \arrow[d] \arrow[dr] & \\
C_{18}H_{11}NO_2 \arrow[d] & C_{18}H_{11}Br \arrow[d] & C_{18}H_{11}COCH_3 \arrow[ddl] \\
C_{18}H_{11}NH_2 \arrow[dr] & C_{18}H_{11}CN \arrow[d] & \\
 & C_{18}H_{11}COOH &
\end{tikzcd}
$$

We were unable to isolate any pure derivative of II after reaction with lead tetraacetate (14) and the hydrocarbon was recovered unchanged after treatment with N-methylformanilide (15).

Benzo[c]phenanthrene (II), and several of its alkyl derivatives couple with *p*-nitrobenzenediazonium chloride in acetic acid (16) quite rapidly. However, the highly carcinogenic 5-methyl derivative, weakly active parent hydrocarbon (II), inactive 5,8-dimethyl and 5,8-diethyl derivatives, and the 1-methyl compound of as yet unknown activity, all coupled at the same rate and gave solutions of the same color. The color was an orange-brown, which would place these compounds in the moderately active group, whereas the rapid rate of color formation would place them in the active group (16). It is thus seen that there is no correlation between carcinogenic activity and response to the diazo coupling test among the derivatives of benzo[c]phenanthrene.

It is a pleasure to acknowledge a grant from the American Cancer Society, recommended by the Committee on Growth of the National Research Council, which greatly assisted in carrying out this research.

EXPERIMENTAL[7]

1-Bromo-2-methylnaphthalene (*III*). This compound prepared in 83% yield by bromination of 2-methylnaphthalene (5), boiled at 117–118° at 2 mm.; n_D^{20} 1.6484; *picrate*, m.p. 114.7–115.1° [literature (17) m.p. 113°].

1-Bromo-2-bromomethylnaphthalene (*IV*). In the best of several runs a mixture of 210 g. (0.95 mole) of 1-bromo-2-methyl-naphthalene, 160 g. (0.90 mole) of N-bromosuccinimide, 1 g. of benzoyl peroxide, and 250 ml. of carbon tetrachloride was refluxed for two and one-half hours. The warm product was filtered after the addition of 250 ml. of carbon tetrachloride, the residue being washed several times with solvent. There was obtained from the filtrate upon concentration and cooling 230 g. (85%) of IV, m.p. 103.5–105.5°. The high temperature (230–240°) bromination of III (5) yielded IV but in yields which never exceeded 59%.

1-Bromo-2-naphthylacetonitrile (*V*). A hot solution of 297 g. (4.57 mole) of potassium cyanide in 400 ml. of water was added to a warm slurry of 682 g. (2.27 mole) of IV in 2.2 l. of

[7] All melting points are corrected; most were taken on a calibrated Fisher-Johns block. All chromatograms were run on 80–200 mesh activated alumina and were of the flowing type. Analyses marked[p] were W. J. Polglase;[k] by E. Klotz;[c] by Clark Microanalytical Laboratories;[a] by Arlington Laboratories;[s] by Sadtler & Sons;[t] by Carl Tiedcke.

absolute alcohol. After heating and stirring for five minutes an exothermic reaction lasting for ten minutes ensued during which much potassium bromide separated. The mixture was further refluxed for 1½ hours and was then poured into 4.5 l of water. The precipitate was collected, washed, dried, and recrystallized from Skellysolve C to yield 400 g. (72%) of V, m.p. 126.2–127.2°, and 45.7 g. (8%) of a second crop, m.p. 119–122°, suitable for hydrolysis. When the reaction was run in the presence of added potassium iodide or at 185–200° in glycerol solution the main product was a substance, m.p. 205.4–205.6°, whose identity has not been established. It is evidently a coupled product, but is not a stilbene type.

1-Bromo-2-naphthylacetic acid, (VI). After refluxing a solution of 424 g. (1.72 mole) of V, 2.5 l. of acetic acid, 500 ml. of concentrated sulfuric acid, and 500 ml. of water for fourteen hours and quenching in 5 l. of ice water, there was obtained 459 g. (100%) of good acid, m.p. 190.0–192.8°. A sample, recrystallized from acetic acid, melted at 196.0–196.2° [lit. (5) m.p. 194°].

α-(1-Bromo-2-naphthyl)-β-phenylacrylic acid, (VII). When a mixture of 10.8 g. (0.038 mole) of the sodium salt of VI, 5.3 g. (0.05 mole) of benzaldehyde, 2.5 g. (0.018 mole) of potassium carbonate, 0.5 ml. of pyridine, and 14 g. (0.125 mole) of acetic anhydride was heated with stirring an exothermic reaction soon took place. After maintaining the mixture at 150–155° for three hours, it was poured into water. The organic residue was digested with hot concentrated sodium hydroxide solution. The insoluble sodium salt was then taken into a large volume of water and freed of neutral material by ether extraction. The acid obtained on acidification melted at 189–196°. Recrystallization from aqueous alcohol afforded 6.6 g. (50%) of VII, m.p. 205–206° [literature (4) m.p. 206–207°]. In large scale runs it is important to add the acetic anhydride to the other components slowly to prevent excessive foaming. By following Hewett's directions (4), we obtained only a 15% yield. Attempts to use acetamide or potassium *t*-butoxide as catalysts were not encouraging.

6-Benzo[c]phenanthrene carboxylic acid, (VIII). This acid was obtained in 54% yield by the reported procedure (4).

Benzo[c]phenanthrene(II). A mixture of 2 g. (7.3 mmoles) of VIII and 0.15 g. of catalyst 37KAF (8) was heated at 295–300° for one hour, during which time 61% of the theoretical amount of carbon dioxide was evolved. Vacuum distillation afforded 1.48 g. (88%) of crude II as a yellow oil, b.p. 175–180° at 0.3 mm., which crystallized on standing and melted at 64.5–67.3°. A sample, purified for biological testing, formed colorless needles, m.p. 67.4–68.0°. The *picrate* (19) was obtained in the form of dark red needles, m.p. 125.9–126.3°. The *TNF complex* formed orange needles, m.p. 170.8–171.1°, from alcohol-benzene.

Anal. Calc'd for $C_{31}H_{17}N_3O_7$: N, 7.8. Found[P]: N, 7.9, 7.8.

By following Hewett's procedure (4), a 79% yield of II was obtained (refluxed one half hour at 160–170° with copper-bronze and quinoline) from VIII.

5-Bromobenzo[c]phenanthrene(IX). A solution of 456 mg. (2 mmoles) of II and 320 mg. (2 mmoles) of bromine in 3 ml. of carbon tetrachloride was held at 40–50° until the evolution of hydrogen bromide ceased (3½ hours). The reaction solution was washed with alkali, dried over calcium sulfate (Drierite), diluted with one-half a volume of petroleum ether, b.p. 65–70° (Skellysolve B), and chromatographed over alumina. The most rapidly eluted fraction, A, yielded 562 mg. of a partly crystalline product which was followed by a smaller fraction, B, of 52 mg. Fraction A was treated with a benzene-alcoholic solution of trinitrofluorenone and the solid complex thus formed was fractionally recrystallized to yield 734 mg. (equivalent to a 59% yield of monobromobenzo[*c*]phenanthrene) of light orange micro-crystals, m.p. 167.4–170.5°.

A sample recrystallized from benzene-alcohol for analysis melted at 170.2–171.4°. A mixed m.p. with the *TNF complex* of II melted at 140–153°.

Anal. Calc'd for $C_{31}H_{16}BrN_3O_7$: N, 6.7. Found[k]: N, 6.5, 6.5.

Similar treatment of fraction B yielded 34 mg. of a *TNF complex*, m.p. 105–108°, which on recrystallization for analysis yielded fine orange needles, m.p. 116.0–117.0°.

Anal. Calc'd for $C_{31}H_{15}Br_2N_3O_7$: N, 6.0. Found[k]: N, 5.7, 5.5.

On chromatographic purification over alumina, the complex from A yielded pure 5-bromobenzo[*c*]phenanthrene as colorless rosettes, m.p. 76.6–77.6°.

Anal. Calc'd for $C_{18}H_{11}Br$: C, 70.4; H, 3.6. Found[k]: C, 70.0; H, 3.9.

Similar treatment of the complex from B yielded a few mg. of crystals, m.p. 169–173°, but too little was obtained for further study.

5-Cyanobenzo[c]phenanthrene(X). A mixture of 90 mg. (0.29 mmoles) of IX, 39 mg. (0.43 meq) of cuprous cyanide, a trace of anhydrous cupric sulfate, and 2 ml. of dry pyridine was heated in a sealed tube at 220–230° for 8½ hours. By chromatographing a benzene solution of the reaction products, there was isolated from the least strongly adsorbed material 56 mg. (76%) of X, m.p. 121–124°. Recrystallization from alcohol yielded colorless needles, m.p. 129.5–129.8° [literature (11) 128–129°].

5-Benzo[c]phenanthrene carboxylic acid(XI). A small amount of the above nitrile (15 mg.) was hydrolyzed by refluxing for twenty hours with 0.9 ml. of acetic acid, 0.2 ml. of sulfuric acid, and 0.2 ml. of water. The product was purified by crystallization of the sodium salt followed by conversion to the acid and sublimation. The m.p. and mixed m.p. with an authentic sample[8] of XI (12) were constant at 238.1–239.2°.

5-Nitrobenzo[c]phenanthrene(XII). A solution of 2.28 g. (10 mmoles) of II, 0.6 ml. of concentrated sulfuric acid, and 0.63 g. (10 mmoles) of nitric acid in 5 ml. of acetic acid was allowed to stand for one hour at room temperature and was then poured into water. The yellow precipitate was collected, dried, dissolved in Skellysolve B—benzene, 1:3, and chromatographed over alumina. The least strongly absorbed material was fractionally crystallized to yield 1.47 g. (54%) of XII as yellow crystals, m.p. 141.5–142.1°. From other eluates, two other compounds were obtained which proved to be dinitro derivatives. These melted at 249.2–251.3° and 212–217° respectively, the latter being isolated in only very small yield.

Anal. Calc'd for $C_{18}H_{11}NO_2$: C, 79.1; H, 4.1. Found[t]: C, 79.2, 79.4; H, 4.5, 4.3.

Calc'd for $C_{18}H_{10}N_2O_4$: C, 67.9; H, 3.2. Found[t]: (250° isomer) C, 67.2; 67.4; H, 3.6, 3.4. (215° isomer) C, 68.0; H, 4.4.

5-Aminobenzo[c]phenanthrene(XIII). (a). By reduction of the 5-nitro derivative. To a refluxing solution of 110 mg. (0.4 mmole) of XII in 100 ml. of absolute alcohol was added a solution of 2.04 g. (10% excess) of 20% aqueous titanous chloride and 2 ml. of concentrated hydrochloric acid. Decolorization was instantaneous. About 70 ml. of solvent was allowed to distil and the remaining solution made slightly alkaline with 2 *M* methanolic potassium hydroxide. After removing the precipitated oxide, the amine was isolated by ether extraction, taken into carbon tetrachloride—benzene, 5:1, and chromatographed on alumina. The fractions which ran through first, using the same solvent pair in ratio 5:1 and then 1:1 were small in weight and were discarded. On elution with benzene-methanol, 70:1 and then 1:1, 74 mg. of material was isolated. Since this would not crystallize or form a crystalline acetate, it was treated with TNF. A brown crystalline complex separated. This was recrystallized to a constant melting point of 195.8–196.2° and proved to be identical to the complex formed from the amine prepared by a Curtius degradation from XI.

Anal. Calc'd for $C_{31}H_{18}N_4O_7$: C, 66.7; H, 3.3; N, 10.0.

Found[c]: C, 66.8; H, 3.3; N, 10.2.

Attempts to reduce the nitro compound with sodium hydrosulfite, with activated iron (20), and catalytically (21) proved unsatisfactory.

(*b*) *By degradation of VIII.* To a cold solution of 500 mg. (1.7 mmoles) of the acid chloride of VIII (prepared in 95% yield with thionyl chloride) in 15 ml. of acetone was added in the cold with shaking, a solution of 150 mg. (2.3 mmoles) of sodium azide in 0.75 ml. of water. After standing in an ice-bath for twenty minutes, the reaction mixture was diluted with water and the precipitated azide was collected and dried to yield 445 mg. of a product which melted at 69–72° decomp. The azide was decomposed by boiling in toluene solution for 2½ hours. Since this solution still gave a positive test for undecomposed azide (22), the toluene was replaced by xylene and the solution refluxed for one hour. The reaction

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[8] This sample was prepared by the procedure cited in (12) with the exception of the condensation between 1-bromo-2-naphthaldehyde and sodium phenylacetate which was effected in 59% yield by the method described for the preparation of VII.

mixture was heated with 10 ml. of 50% potassium hydroxide for fifteen minutes. A small amount (101 mg.) of tan solid, m.p. 240–249°, separated but was not further examined. The xylene layer was dried and treated with dry hydrogen chloride to yield 217 mg. of amine hydrochloride, m.p. 192–209°. Since this proved difficult to purify, it was converted to the free amine. The *TNF complex* prepared from this formed brown needles, m.p. 195.8–196.2°. The mixed melting point with the TNF complex prepared as under (a) above was not depressed.

5-Benzo[c]phenanthryl methyl ketone(XIV). To a stirred solution at room temperature of 228 mg. (1 mmole) of II and 102 mg. (1 mmole) of acetic anhydride in 2 ml. of chlorobenzene was added in six portions 280 mg. (2.1 mmoles) of aluminum chloride. After stirring for three hours, the mixture was hydrolyzed and the dried green chlorobenzene solution was poured on to an alumina column. Upon developing and eluting with first, carbon tetrachloride-benzene, 1:1; secondly, benzene; and finally, benzene-1% methanol, fractions A and C crystallized. From A was isolated a small amount of unchanged benzo[c]phenanthrene. From C was obtained 100 mg. of almost colorless prisms of XIV, m.p. 109.8–110.5°, after two recrystallizations from alcohol (literature (11) m.p. 111.5–112.5°). The *semicarbazone,* prepared by the Hopper method (23), melted at 234–234.5° with decomp. (literature (11) m.p. 235–236°).

Attempts to prepare an acetyl derivative of II using acetyl chloride produced only high melting compounds in complex mixture. No acetylation of II occurred on heating II, acetic anhydride, benzene, and 85% phosphoric acid (24) at reflux for 2½ hours.

To a boiling solution of 46 mg. of XIV in 1 ml. of pyridine was added during ten minutes 1.5 ml. of a potassium hypochlorite solution (25) containing a slight excess of oxidizing agent. The color of the solution darkened to deep cherry red and then lightened to yellow. After refluxing two minutes more, a saturated solution of sodium bisulfite was added to destroy excess hypochlorite. The acid fraction was taken into alkali and treated with decolorizing carbon (Dareo G-60). The crude acid thus obtained was recrystallized to a melting point of 238–239° and on mixing with an authentic sample (12) of XI, no depression was observed.

Reactions of II and homologs with diazotized p-nitraniline. Ten drops of a solution of *p*-nitrobenzenediazonium chloride (26) was added to a solution of 5 mg. of the compound to be tested in ten drops of acetic acid. The colors all formed within five seconds and were of approximately the same intensity. No change was noted after twelve hours. A blank test gave a light yellow color. The following alkyl derivatives of II and III all gave the same orange-brown color: 1-methyl-, 5-methyl-, 5,8-dimethyl-, and 5,8-diethyl- (19).

α-(1-Bromo-2-naphthyl)-β-phenylacrylonitrile(XV). To an agitated mixture of 1.8 g. (7.3 mmoles) of 1-bromo-2-naphthylacetonitrile, 5 ml. of dioxane, 0.2 g. (5.1 mmoles) of potassium, and 4 ml. of *t*-butyl alcohol was added 1.8 g. (17 mmoles) of benzaldehyde. The purple mixture was heated on the steam-bath for fifteen minutes, poured into water, acidified, and extracted with ether. After the ethereal layer had been washed with saturated sodium bisulfite and sodium chloride solutions, removal of the solvent left 1.17 g. (53%) of nitrile, m.p. 82–94°. Sodium ethoxide was an inferior catalyst (4) (27) and sodium amide (28) was inactive.

Attempted hydrolysis of XV. (*27b*) (*29*) A mixture of 15 ml. of 10% hydrogen peroxide, 1.2 g of XV, 8 ml. of 10% sodium carbonate solution, and 25 ml. of acetone was heated at 45–55° for fourteen hours, refluxed for 2½ hours, and then poured into water to yield XV unchanged. 1-Bromo-2-naphthylacetonitrile was hydrolyzed under the same conditions. A hydrolytic mixture of sulfuric acid, acetic acid, and water was also ineffectual.

SUMMARY

It is shown that the most reactive position of benzo[*c*]phenanthrene is position 5. A monobromo, mononitro, and monoacetyl derivative of benzo[*c*]phenanthrene have been prepared and each shown to be the 5-isomer.

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[Contribution from the University of Cincinnati]

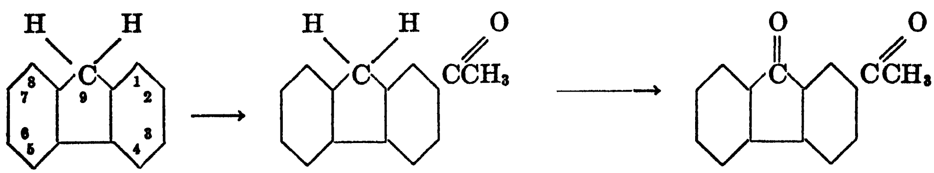
FLUORENE DERIVATIVES FOR CANCER RESEARCH[1]

SIDNEY SCHULMAN[2]

Received December 3, 1948

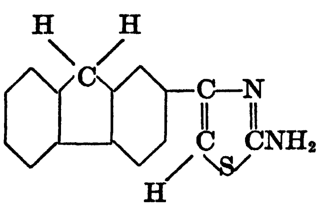
During toxicity tests, Wilson, De Eds, and Cox (1) discovered that 2-acetamidofluorene and 2-aminofluorene possessed carcinogenic activity. This discovery has led to a program of synthesis to test other derivatives of the fluorene molecule for carcinogenic activity, as well as for possible cancer therapeutic action. During the work on a portion of this program a number of new fluorene compounds were prepared and a number of existing syntheses improved.

According to Dodson and King (2) ketones having two active α-hydrogens condense with thiourea in the presence of free halogen to give 4-substituted-2-aminothiazoles. Accordingly, fluorene was acetylated with acetic anhydride to yield 2-acetylfluorene, I. The latter compound was oxidized with sodium dichromate to 2-acetylfluorenone, II. The methyl ketones were condensed with thiourea in



I II

the presence of iodine. The resulting 4-(2-fluorenyl)-2-aminothiazole and 4-(2-fluorenyl-9-one)-2-aminothiazole hydroiodide salts were isolated, and the corre-



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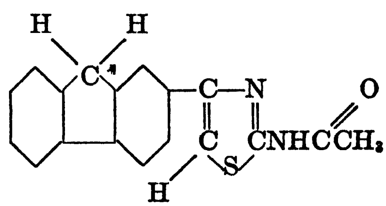
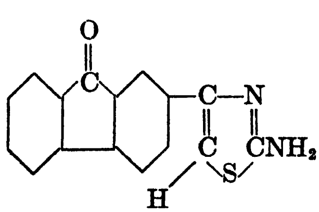


IV



V

[1] From a part of the thesis submitted to the graduate faculty of the University of Cincinnati in partial fulfilment of the requirements for the degree of Doctor of Philosophy, June, 1948.

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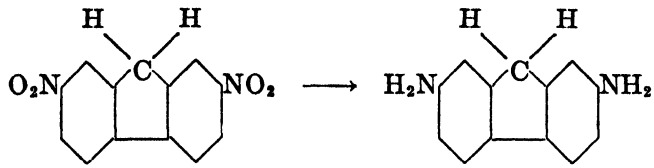
sponding free amines, III, V, then liberated by means of ammonium hydroxide. In order to characterize the amino group, 4-(2-fluorenyl)-2-aminothiazole was acetylated with acetic anhydride to yield 4-(2-fluorenyl)-2-acetamidothiazole, IV.

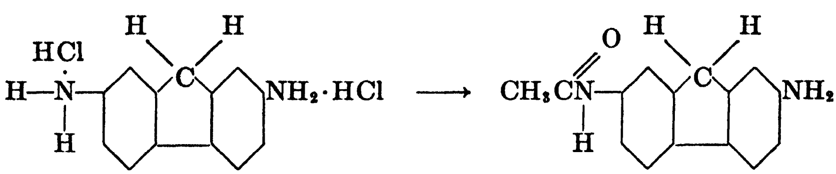
When 2,7-dinitrofluorene, VI, was reduced to 2,7-diaminofluorene, VII, as described by Diels (3), the isolation of the diamine from the reaction products



VI VII

was not only cumbersome and time consuming, but gave poor yields. A simpler method of isolation of 2,7-diaminofluorene from its reaction products was devised, with yields of 90%, based on the amount of 2,7-dinitrofluorene used. A tin-2,7-diaminofluorene complex was crystallized from the partially distilled mother liquor. Dilute sulfuric acid decomposed the complex, and precipitated the sulfate of the diamine. Ammonium hydroxide liberated the free amine from its salt.

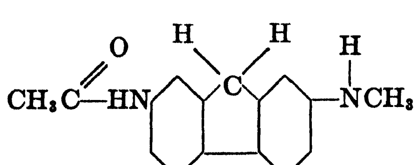
Cislak and Hamilton (4) synthesized 2-amino-7-acetamidofluorene, IX, by reducing 2-nitro-7-acetamidofluorene. However a purer product in larger yields was obtained by the addition of stoichiometric amounts of acetic anhydride to 2,7-diaminofluorene dihydrochloride, VIII. The 2-amino-7-acetamidofluorene hydrochloride was converted to the free amine with dilute ammonium hydroxide. The addition of stoichiometric amounts of 2,7-diaminofluorene and acetic anhydride in neutral anhydrous organic solvents led to mixtures of 2,7-diacetamido-



VIII IX

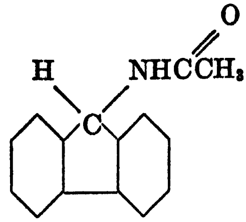
fluorene and the acetic acid salt of the diamine. Evidently the monoacetic acid salt was less basic than the monoacetylated diamine.

A new fluorene derivative, 2-N-methylamino-7-acetamidofluorene, X, was syn thesized by treatment of a suspension of 2-amino-7-acetamidofluorene in benzene with dimethyl sulfate.



X

Langecker (5) reported that 9-acetamidofluorene, XI, melted at 246°, while

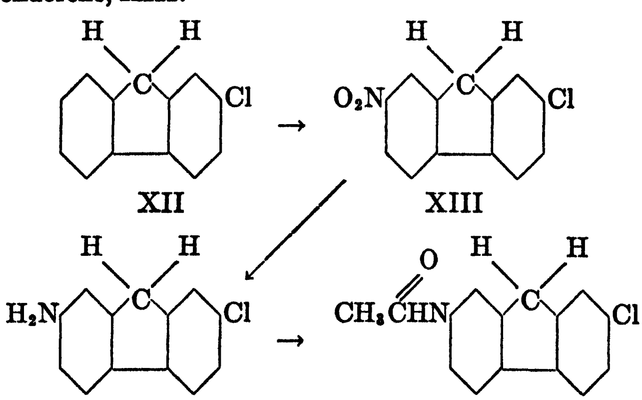


XI

Schmitt (6) and Goldschmidt (7), using similar methods of production and acetic acid as the crystallization medium reported a melting point of 261°. Using a similar process, the same solvent for recrystallization and employing slow crystal growth, the author has found that 9-acetamidofluorene melted at 246°, as reported by Langecker. The apparent anomaly in melting point may be due to heteromorphic crystalline forms. This phenomenom sometimes occurs in the fluorene series when different rates of crystal formation or various solvents are used.

The synthesis of 2-nitrofluorene was greatly facilitated by modifying the experimental technique as described in Organic Syntheses (8). Using accurate temperature control rather than a water-bath, the nitrating agent was added rapidly instead of dropwise, thus saving considerable time. The exothermic reaction was also easier to control without the use of a water-bath.

2-Chloro-7-acetamidofluorene, XV, was synthesized by the acetylation of 2-chloro-7-aminofluorene, XIV, with acetic anhydride. The latter derivative was obtained by reduction of the corresponding nitro compound with zinc and calcium chloride in alcoholic solution. The direct chlorination of fluorene to produce 2-chlorofluorene, XII, followed by nitration in glacial acetic acid, yielded 2-chloro-7-nitrofluorene, XIII.



XII XIII XIV XV

The biological testing of these compounds is being carried out at the Sloan-Kettering Institute for Cancer Research in New York City, and the findings will be published later.

I should like to thank the Sloan-Kettering Institute for Cancer Research and the University of Cincinnati for the funds allocated to this project.

EXPERIMENTAL

All melting points are uncorrected.

2-Nitrofluorene. The process recommended in Organic Syntheses (8) for the production of this compound has been modified to facilitate the temperature control and to increase the speed of production.

One liter of glacial acetic acid and 120 grams (0.72 mole) of fluorene (m.p. 107–110°) were introduced into a 2-liter 3-neck flask, equipped with a Hershberg mechanical stirrer, a thermometer, and a dropping-funnel. The suspension was stirred vigorously and heated until all the fluorene dissolved. The temperature was adjusted to 60–65°, and 160 ml. of concentrated nitric acid (sp. gr. 1.42) added in a slow steady stream. The temperature rose quickly and during this period the mixture was stirred vigorously. The temperature was not allowed to rise above 80°. A yellow precipitate separated and formed a paste. The vigorous stirring was continued to dissipate the heat, until the temperature dropped to about 60°. (When the temperature began to fall the dropping-funnel was replaced by a suction tube to draw off the oxidizing gases.) The product was filtered, sucked as dry as possible, washed with two 50-ml. portions of glacial acetic acid, each containing one gram of potassium acetate, and then with 50 ml. of glacial acetic acid. The 2-nitrofluorene was washed twice by covering with 1.5 liters of water, stirring mechanically for a few minutes, filtering, and air drying; yield 120 grams, m.p. 156–157°.

2-Acetylfluorene (I). This compound was synthesized according to the directions of Ray and Rieveschl, Jr. (9) except that double quantities were used.

2-Acetylfluorenone (II). This oxidation was carried out as described by Ray and Rieveschl, Jr. (9).

4-(2-Fluorenyl)-2-aminothiazole hydroiodide. Eighty grams (0.38 mole) of 2-acetylfluorene (m.p. 126°), sixty grams (0.86 mole) of thiourea, and 450 ml. of dioxane (peroxide free) were heated on a water-bath and 100 grams (0.40 mole) of iodine added during 2.5 hours. Heating was continued for 20 hours and after cooling an orange precipitate was filtered. The precipitate turned white upon washing with alcohol; yield 100 g. After recrystallization from 60% acetic acid the product sintered at 290° and melted to a red liquid at 306°.

4-(2-Fluorenyl)-2-aminothiazole (III). Twenty grams of 4-(2-fluorenyl)-2-aminothiazole hydroiodide was covered with 60 ml. of 10% alcoholic ammonia, the suspension mechanically stirred, filtered, and the precipitate washed with a little alcohol; m.p. 256°. The product was recrystallized from nitrobenzene (during the recrystallization an atmosphere of nitrogen was provided, otherwise oxidative impurities formed), washed with alcohol, and dried in a vacuum desiccator, or under an atmosphere of nitrogen; yield 14 g., m.p. 263°.

Anal. Calc'd for $C_{16}H_{12}N_2S$: N, 10.61. Found: N, 10.28.

4-(2-Fluorenyl)-2-acetamidothiazole (IV). Twenty grams of 4-(2-fluorenyl)-2-aminothiazole and 100 ml. (1.0 mole) of acetic anhydride were slowly brought to reflux, while being mechanically stirred. The suspension was refluxed 30 minutes, cooled, poured into 1.5 liters of cold water, and allowed to react for two hours. The suspension was filtered and the precipitate was washed with distilled water and then with acetone. The dry product sintered at 280°; m.p. 304–305°. After recrystallization from acetophenone the compound turned brown at 285°, melting at 304–305°; yield 16 g.

Anal. Calc'd for $C_{18}H_{14}N_2OS$: N, 9.15. Found: N, 8.91.

4-(2-Fluorenyl-9-one)-2-aminothiazole hydroiodide. Twenty five grams (0.11 mole) of 2-acetylfluorenone (m.p. 153–154°), 15 grams (0.23 mole) of thiourea, 130 ml. of dioxane (peroxide free), and 28 grams (0.11 mole) of iodine were heated on an oil-bath (*ca.* 115°) so the dioxane was in gentle reflux. The reaction mixture was cooled and filtered. The pre-

cipitate, when washed with a little alcohol, turned bright yellow; yield 25 g., sintered 195°, m.p. 303°.

4(-2-Fluorenyl-9-one)-2-aminothiazole (V). Sodium hydroxide (6 *N*) was added dropwise to an aqueous slurry of the yellow hydroiodide salt until the slurry was distinctly alkaline. The reaction mixture was filtered and the now red precipitate was dissolved in hot alcohol. The alcohol solution was filtered and 3x the volume of water was slowly added, with stirring. A red precipitate formed; sintered *ca.* 190°, m.p. 195–200°. The product was recrystallized from xylene (4 grams/100 ml. xylene); sintered 194°, m.p. 198–201°.

Anal. Calc'd for $C_{16}H_{10}N_2O$: N, 10.07. Found: N, 9.96.

2,7-Dinitrofluorene (VI). The best product was obtained by the method of Courtot (10), using yellow fuming nitric acid (sp. gr. 1.52) as the nitrating agent.

2,7-Diaminofluorene (VII). A suspension consisting of 50 g. of 2,7-dinitrofluorene (VI), 800 ml. of alcohol, 250 ml. of concentrated hydrochloric acid (sp. gr. 1.19), and 250 g. of granulated tin was refluxed until all the 2,7-dinitrofluorene had been reduced, about 2–3 hours. The reaction was filtered and 500 ml. of the solvent distilled off. The concentrated solution was allowed to cool and cream-colored tin complex salt crystals separated. The crystals were filtered, covered with 400 ml. of 3 *N* sulfuric acid, mechanically stirred, and again filtered. This precipitate was returned to a beaker, suspended in 100 ml. of water, and concentrated ammonium hydroxide added dropwise until the suspension was distinctly alkaline. Then 400 ml. of 3 *N* sulfuric acid was added slowly, the suspension stirred well, filtered, and the precipitate washed twice with 50 ml. of water. The free amine was liberated by suspending the sulfate in a mixture of 300 ml. of water and 100 ml. of concentrated ammonium hydroxide; yield 34 g., m.p. 163–164°.

2,7-Diaminofluorene dihydrochloride (VIII). 2,7-Diaminofluorene, VII, was dissolved in boiling xylene, filtered, and cooled. Dry HCl gas was passed in until no more material precipitated. The white product was filtered, washed with ether and dried, m.p. above 300°.

2-Amino-7-acetamidofluorene (IX). Thirty-five grams (0.13 mole) of 2,7-diaminofluorene dihydrochloride, VIII, was suspended in 1100 ml. of water and the suspension stirred rapidly and heated (60–70°) until all the precipitate dissolved. The clear solution was then cooled rapidly to room temperature and 13.00 ml. (0.13 mole) of acetic anhydride added dropwise, during the course of 30 minutes, with constant stirring. After all the acetic anhydride was added the mixture was stirred 60 minutes longer, then filtered, and the precipitate washed with a little water. The precipitate was placed in a beaker, covered with 400 ml. of water, and 75 ml. of concentrated ammonium hydroxide added slowly to the well-stirred suspension. The product was filtered and washed with water; sintered 125°, m.p. 140°. After three recrystallizations from alcohol the product melted at 198–199°; yield 20 g. The product was analyzed as the *hydrochloride.*

Anal. Calc'd for $C_{15}H_{15}ClN_2O$: N, 10.22. Found: N, 10.32.

The remaining 2,7-diaminofluorene was recovered by adding 10 ml. of concentrated hydrochloric acid to the mother liquor and refluxing for 20 minutes. The solution was cooled, made alkaline with ammonium hydroxide, and filtered; m.p. 162–164°.

2-N-Methylamino-7-acetamidofluorene (X). Thirty grams (0.126 mole) of 2-amino-7-acetamidofluorene, IX, was suspended in 1500 ml. of benzene and 45 grams (0.36 mole) of dimethyl sulfate added dropwise. The suspension was refluxed for ninety minutes and after cooling a light grey precipitate was filtered, m.p. above 300°. This product was stirred with ammonium hydroxide, filtered, washed with water, dried, and recrystallized from acetone. It melted to a gel *ca.* 105–110°. After one recrystallization from absolute alcohol the product sintered at 185°; m.p. 190–196°. Repeated recrystallizations from absolute alcohol gave a constant melting point of 203–204°; yield 4 g. A mixture of pure 2-amino-7-acetamidofluorene and the product sintered at 155–160°; m.p. 180–185°.

Anal. Calc'd for $C_{16}H_{16}N_2O$: N, 11.12. Found: N, 11.00.

9-Acetamidofluorene (XI). Forty grams (0.20 mole) of 9-fluorenone oxime (11) in 350 ml. of glacial acetic acid was reduced with 50 g. (0.77 mole) of zinc dust, added in small incre-

ments over a period of 30 minutes. The mixture was refluxed for an hour and after 55 ml. (0.55 mole) of acetic anhydride was added dropwise to the boiling solution it was refluxed again for an hour, filtered hot, and allowed to cool. White crystals settled out which were filtered and washed with acetic acid; yield 45 g., m.p. 246°. Subsequent recrystallization from acetic acid did not alter the melting point.

Anal. Calc'd for $C_{15}H_{13}NO$: N, 6.28. Found: N, 6.17.

2-Chlorofluorene (*XII*). This intermediate was synthesized according to the procedure of Courtot (10).

2-Chloro-7-nitrofluorene (*XIII*). The procedure was the same as that described for 2-nitrofluorene, I. The quantity of reactants used was 88 g. (0.44 mole) of 2-chlorofluorene, 810 ml. of glacial acetic acid, and 120 ml. of nitric acid (sp. gr. 1.42); yield 70 g. The crude product sintered at 210–220°; m.p. 222–235°. The product was recrystallized twice from glacial acetic acid; m.p. 243–244°. Courtot (10) found m.p. 237° (recrystallized from benzene).

2-Chloro-7-aminofluorene (*XIV*). Ten grams (0.04 mole) of 2-chloro-7-nitrofluorene (m.p. 243–244°) and 100 grams of zinc dust were suspended in 400 ml. of alcohol and 70 ml. of water. The suspension was refluxed for 2 hours, filtered hot, and poured into 3 liters of water; m.p. 136–138°. The product was recrystallized from 50% alcohol, with Darco; yield 7 g., m.p. 139°.

2-Chloro-7-acetamidofluorene (*XV*). Seven grams of 2-chloro-7-aminofluorene was dissolved in 100 ml. of hot glacial acetic acid and 20 ml. (0.20 mole) of acetic anhydride added dropwise to the refluxing solution. The solution was refluxed for 20 minutes and cooled, whereupon a white crystalline product settled out; yield 7.6 g., m.p. 228–230°. Recrystallization from glacial acetic acid gave the constant melting point 230–231°.

Anal. Calc'd for $C_{15}H_{12}ClNO$: N, 5.45. Found: N, 5.23.

SUMMARY

A number of new fluorene derivatives have been prepared and the synthesis of several other fluorene compounds has been simplified.

CINCINNATI, OHIO

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[Contribution from the Sterling-Winthrop Research Institute]

THE USE OF DIAZO COMPOUNDS IN THE PREPARATION OF SOME BENZYLPENICILLIN ESTERS[1]

FRED K. KIRCHNER, J. R. McCORMICK,[2] CHESTER J. CAVALLITO, and LLOYD C. MILLER

Received December 10, 1948

In a previous publication (1) interest was indicated in the preparation of benzylpenicillin esters and the results of preliminary tests with the benzyl ester were given. The program was initiated with the hope that some derivative of penicillin would be found which would be more suitable than the salts of benzylpenicillin for oral administration and which would have a depot action on injection. Table I shows the data for the esters reported in this paper. The preparation of crude methyl, ethyl, and *n*-butyl esters has been reported previously (2, 3).

Because of the instability of the penicillin molecule the more common methods of esterification (acid with an alcohol, acid chloride with an alcohol or an alkoxide, etc.) could not be used. Therefore, a milder esterifying agent, the diazoalkanes, was chosen. The esters were prepared by treating free benzylpenicillin in an organic solvent with an excess of the appropriate diazo compound and isolating the pure ester.

The diazo compounds were prepared by an adaptation of Werner's method (4) in which the nitrosourea was decomposed at a low temperature with aqueous potassium hydroxide solution in the presence of an inert immiscible solvent to take up the product.

The necessary ureas were prepared from the corresponding amines by the nitrourea reaction (5) or, when the product was relatively water insoluble, by fusion of the amine with excess urea and isolation of the substituted urea by leaching with water (6).

Nitrosation of the substituted ureas was effected at low temperature using sodium nitrite and acetic acid.

Since the penicillin esters prepared with the usual diazo compounds were water-insoluble, interest was centered in the problem of introducing a group which would make the resulting ester more water-soluble. There was the possibility that such an ester might exhibit variations from the usual benzylpenicillin antibacterial "spectrum." For this purpose there was prepared an ester using 2-(2-pyridyl)diazoethane. The 2-(2-aminoethyl)pyridine used in the preparation of the diazo compound was prepared essentially by Galat's method (7). Further interest in a basic diazo compound stems from the fact that few diazo compounds are known which contain a basic ring-nitrogen. Thus, d'Angelo and

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his co-workers (8, 9) reported some diazoindoles, while Angelico reported diazopyrroles (10). No reference has been found in which diazo compounds containing a pyridine ring have been recorded.

An attempt was made to prepare basic diazoalkanes in which the basic nitrogen was not part of a ring. For this purpose 2-dimethylaminoethyl urea (11) and 3-diethylaminopropyl urea were prepared. However, the usual nitrosation procedure (with nitrous acid) did not yield any of the nitrosourea. In another attempt the preparation of *p*-dimethylaminophenylmethyldiazomethane was undertaken by preparing the ketazine from *p*-dimethylaminoacetophenone and hydrazine sulfate, using the procedure of Curtius and Franzen (12). The ketazine was converted to the hydrazone with anhydrous hydrazine and the hydrazone oxidized with yellow mercuric oxide (13). The preparation of *p*-dimethylaminophenyldiazomethane also was attempted, using anhydrous hydrazine to prepare the hydrazone and then oxidizing it with mercury acetamide (14). However, if any diazo compound was formed it was unusually unstable, for the red ether solution soon began to precipitate a decomposition product.

The use of 2-(2-pyridyl)diazoethane and 2-phenyldiazoethane is reported for the first time. Adamson and Kenner (15) had prepared diazoethane, diazopropane, diazo-*n*-butane, 3-methyldiazobutane, and diazopropene-2 using the corresponding nitrosoalkylaminomesityl oxide as an intermediate. Phenyldiazomethane was reported by Werner (4), who utilized the action of an alkali upon nitrosobenzyl urea, and by Staudinger (13), who oxidized benzalhydrazone with mercuric oxide. The preparation of diazomethane has been reported numerous times (16, 17).

Antibiotic action. Serial dilution tests indicate that the neutral esters are considerably less active *in vitro* than the benzylpenicillin salt (1). Since the solubility of the neutral esters in aqueous media is very low, accurate comparisons are difficult to make. The pyridylethyl ester can be prepared in solution as the hydrochloride (3 mg. per ml. pH 3.5) and tested by serial dilution in broth.[3]

The results of *in vivo* mouse-protection tests (1) with *Streptococcus hemolyticus* are summarized in the table.[4] These results are from one hour post-infection subcutaneous administration of the ester in sesame oil. Further tests indicate that considerable species specificity is evidenced in the protection of animals with benzylpenicillin esters. This appears to be related to the ability of the animal serum to hydrolyze the ester with the liberation of free benzylpenicillin.

Mr. W. F. Warner of these laboratories has shown that mouse and rat sera hydrolyze these esters to free benzylpenicillin, whereas rabbit, dog, and human sera do not have this property. These results are in agreement with those recorded by other workers (18, 19, 20).

[3] Tests by Dr. John Hays Bailey of these laboratories indicate comparable activity with this ester and benzylpenicillin salts against *Staphylococcus aureus* 209, and one-thirtieth the activity was displayed against *Bacillus subtilis* and *Streptococcus hemolyticus B*.

[4] The *in vivo* tests were carried out by Mr. H. Grunwald and Miss M. Shibuya.

EXPERIMENTAL[5]

Alkyl ureas. The ethyl, *n*-propyl, *n*-butyl, isobutyl, and allyl ureas were prepared by means of the nitrourea reaction (5).

Aralkyl ureas. The benzyl and 2-phenethyl ureas were prepared following essentially the method of Davis and Blanchard (6).

Nitrosoureas. The monosubstituted ureas, ethyl, *n*-propyl, *n*-butyl, isobutyl, allyl, phenethyl, and benzyl were nitrosated as follows: two-tenths mole of the substituted urea was dissolved in 100 ml. of glacial acetic acid and 15 ml. of water, and the solution cooled to 10° or less. To this cold solution was added from a dropping-funnel a solution of 28 g. (0.4 mole) of sodium nitrite in 60 ml. of water. The rate of addition was such that all of the

TABLE I

BENZYLPENICILLIN ESTERS

ESTER	CARBON, %		HYDROGEN, %		NITROGEN, %		DOSAGE FOR COMPLETE PROTECTION, MG. PER MOUSE[b, c]
	Calc'd	Found	Calc'd	Found	Calc'd	Found	
Methyl[a]	58.60	58.46	5.79	6.17	8.04	8.09	0.05
Ethyl	59.65	59.81	6.12	6.22	7.73	7.92	.05
n-Propyl	60.61	60.26	6.43	6.71	7.44	7.58	.05
n-Butyl	61.51	61.68	6.71	6.87	7.17	7.42	.01
Isobutyl	61.51	61.21	6.71	6.75	7.17	7.10	.02
Allyl	60.94	61.33	5.92	6.16	7.48	7.25	.03
Benzyl	65.07	65.26	5.69	5.57	6.59	6.61	.01
Phenethyl	65.73	65.65	5.98	6.15	6.39	6.50	.05
2-(2-Pyridyl)ethyl	62.85	63.05	5.73	5.36	9.56	9.38	.01

[a] This ester, m.p. 89.5–92.2° (corr.), has been prepared by other workers. This fact will be reported in the monograph, "*The Chemistry of Penicillin*," Princeton University Press, Princeton, N. J.

[b] Quantity of ester required for protection of 20-g. mice inoculated by the intraperitoneal route with 0.3 cc. of a 1:100,000 dilution of an 18 hour broth culture of *Streptococcus hemolyticus* C203.

[c] Sodium benzylpenicillin protective dose by similar test method is approximately 0.1 mg. per mouse.

nitrite solution was added in four hours. The mixture was diluted with 300 ml. of ice-cold water and the nitrosourea filtered off. After washing on the filter with water, the residue was purified by dissolving in 50 ml. of methanol at reflux temperature and then cooling the solution at 0° with stirring. The precipitate was filtered off and washed on the filter with a cold ether-Skellysolve A mixture (1:1). Yields were 35–55%, based on the substituted urea used. Phenethylnitrosourea, m.p. 100–101° (dec.).

Anal. Calc'd for $C_9H_{11}N_3O_2$: N, 21.76. Found: N, 22.14.

Diazo compounds. To 30 ml. of a cold (0–10°) 50% aqueous potassium hydroxide solution layered with 50 ml. of Skellysolve A was added over a period of ten minutes with constant stirring, 0.05 mole of the substituted nitrosourea. The latter usually was dispersed in the alkali layer as a grey or tan powder. Upon continued stirring for fifteen to thirty minutes

[5] In the experimental section physical constants and analyses are reported only for those compounds which have not been reported previously, and for those whose preparation differs from that found in the literature.

The analytical determinations were done under the direction of Mr. M. E. Auerbach in the Analytical Laboratories of this Institute.

the powder underwent spontaneous decomposition to give the diazo compound which was taken up by the Skellysolve A layer. The color of the latter ranged from yellow to red. Occasionally it was found desirable to initiate the decomposition of the nitrosourea salt by adding slowly 10–20 ml. of water. For the preparation of the esters the Skellysolve A layer was decanted and used directly.

2-(2-Aminoethyl)pyridine. The procedure was patterned after Galat's method (7).

In a two-liter, three-neck, round-bottom flask fitted with a thermometer and condenser were placed 380 g. (2.6 moles) of phthalimide and 276 ml. (2.6 moles) of 2-vinylpyridine. After adding 1 ml. of Triton B to the solution the mixture was heated under reflux until only one phase was present and the batch temperature reached 188° without appreciable refluxing (about two hours). The reaction mixture was cooled to 110° and a total of 500 ml. of chloroform was added in small portions through the condenser. The chloroform solution was cooled to 10°. Any solid precipitating at this point was filtered off. To the cooled chloroform solution was added Skellysolve A during mechanical stirring. The resulting precipitate was filtered with suction and washed with a chloroform-Skellysolve A mixture (1:3) until the washings were clear. By concentrating the mother liquor, cooling, and adding Skellysolve A as before, an additional quantity of precipitate was formed. In this manner there was obtained 511 g. (75%) of N-[2-(2-pyridylethyl)]phthalimide as a tan powder of m.p. 95–97°; m.p. of the hydrochloride was 214–215°.

Anal. Calc'd for $C_{15}H_{13}ClN_2O_2$: C, 62.39; H, 4.54; Cl, 12.28.
Found: C, 62.35; H, 4.41; Cl, 12.29.

In a one-liter round-bottom flask fitted with a stirrer were placed 124 g. (0.47 mole) of the substituted phthalimide and 500 ml. of methanol. After stirring for five minutes, 38.3 g. (0.65 mole) of hydrazine hydrate (85%) was added and stirring was continued for 1.5 hours at room temperature. At the end of this period practically all of the alcohol was removed under reduced pressure. The residue was treated with 400 ml. of water, the mixture stirred, and concentrated hydrochloric acid added slowly until the solution was acid to Congo Red paper. The solution was filtered with suction and the residue washed twice with 50-ml. portions of water. The combined filtrate and washings were made alkaline ($>$ *p*H 10) with 40% aqueous sodium hydroxide solution and the basic solution extracted ten times with 50-ml. portions of chloroform. The chloroform solution was concentrated and after removal of the solvent the resulting residue was distilled at reduced pressure. The yield of amine, b.p. 92–93°/12 mm., was 26.5 g. (46%); reported 92–93°/12 mm. (21). M.p. of the dihydrochloride was 189°; reported, 185–186° (22).

Anal. Calc'd for $C_7H_{12}Cl_2N_2$: Cl, 35.68. Found: Cl, 35.89.

2-(2-Pyridylethyl)urea. Forty-one grams (0.34 mole) of the amine and 43 g. (0.41 mole) of nitrourea were added to 200 ml. of methanol contained in a flask fitted with a reflux condenser. Initial heat was applied cautiously; then gradually the contents were heated to reflux, the refluxing being continued for thirty minutes. After cooling to room temperature, ether was added until the solution became cloudy. On cooling in an ice-bath, crystals of the desired urea were precipitated. The yield of the urea, m.p. 143°, was 30 g. (55%).

Anal. Calc'd for $C_8H_{11}N_3O$: C, 58.18; H, 6.73; N, 25.45.
Found: C, 58.11; H, 6.72; N, 25.34.

2-(2-Pyridylethyl)nitrosourea. Thirty-three grams (0.2 mole) of the urea was added to 200 ml. of water and 65 ml. of concentrated hydrochloric acid. The solution was stirred and cooled to 0–10°, and a solution of 40 g. of sodium nitrite in 90 ml. of water was added dropwise over a period of four hours. The clear solution was extracted once with 25 ml. of chloroform, then neutralized at 5° with a saturated aqueous sodium bicarbonate solution. When the aqueous solution was neutral a precipitate formed which was filtered with suction. The residue on the filter paper was washed twice with cold water, then dried at 0° in a drying chamber. The yield of the nitroso compound, m.p. 108° (dec.), was 15.5 g. (40%).

Anal. Calc'd for $C_8H_{10}N_4O_2$: N, 28.86. Found: N, 28.26.

Crude penicillin esters. Two grams of calcium benzylpenicillin (about 800 units per mg.) was dissolved in 500 ml. of distilled water, 100 ml. of ethyl acetate was added, and the

mixture was cooled at 10°. The cooled solution was acidified by slowly adding phosphoric acid with stirring until pH 2.5 was reached. The mixture was shaken in a separatory funnel, the layers separated, and the aqueous layer extracted again, once with 75 ml. of ethyl acetate, followed by two 100-ml. portions of ether.

To the combined ethyl acetate-ether solution was added an excess of the desired diazo compound dissolved in Skellysolve A (23). The reaction mixture was allowed to stand for three hours at room temperature. At the end of this period any unused diazo compound was decomposed by washing with three 70-ml. portions of 1% citric acid or 1% acetic acid. The ethyl acetate-ether solution was then extracted with as many 50-ml. portions of 1% sodium bicarbonate solution as was necessary to obtain a colorless bicarbonate layer. In general, only one such washing was necessary. The mixture was washed once more with two 50-ml. portions of water and the organic solvents were removed *in vacuo* to give the crude ester.

With the pyridyl ester a slight modification in the above procedure was necessary. After standing for three hours about 50 ml. of the 1% acid solution was added to the reaction mixture to destroy any excess diazo compound. After separating the aqueous layer, it was made alkaline to pH 8 and extracted several times with ethyl acetate. This ethyl acetate extract was added to the original ethyl acetate-ether solution and the latter washed with the bicarbonate solution as outlined above.

Purification of penicillin esters. The crude esters were dissolved in about 15 ml. of ether, warmed slightly on a steam-bath, and Skellysolve B added to the point of turbidity. The flask then was cooled by immersing into a methylene chloride-Dry Ice bath to induce precipitation. During the cooling process the contents of the flask were swirled. The first precipitate obtained was gummy in appearance. The flask was removed from the cooling-bath, allowed to warm slightly, and then after making certain that all of the precipitate adhered to the bottom and sides of the flask, the supernatant liquid was decanted. The residue was redissolved in ether and the above procedure repeated about three more times. In this purification process the precipitate became more flocculent and semi-solid in nature. However, during the warming-up phase of the procedure the semi-solid softened and adhered to the flask so that removal of the supernatant liquid was facilitated. After the final decantation and warming to room temperature there remained a viscous yellow substance. The purified ester was subjected to a high vacuum in the presence of paraffin shavings to help remove the last traces of solvent. With complete removal of the solvent there remained with the exception of the crystalline methyl ester, a highly viscous, and sometimes brittle, substance. When constant weight was obtained the compound was submitted for analysis. The analytical values obtained for carbon and hydrogen were used as a criterion of purity. The preparation of some of these esters using crystalline sodium benzylpenicillin gave similar results.

SUMMARY

1. The following analytically pure benzylpenicillin esters have been prepared: methyl, ethyl, n-propyl, n-butyl, isobutyl, allyl, benzyl, phenethyl, and 2-(2-pyridylethyl).

2. The use of two diazo compounds, 2-(2-pyridyl)diazoethane and 2-phenyldiazoethane, is considered to be reported for the first time.

3. *In vivo* tests indicate that the penicillin esters are generally more effective than sodium penicillin in protecting mice against *Streptococcus hemolyticus.*

4. The ineffectiveness of the esters in higher animals probably is related to the inability of the sera to hydrolyze the esters.

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[Contribution from the Laboratory of Radiochemistry,
University of Cincinnati]

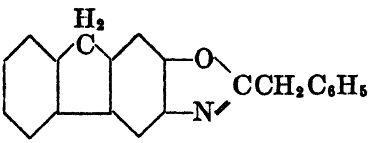
FLUORENE OXAZOLES

FRANCIS EARL RAY and CHARLES F. HULL

Received December 10, 1948

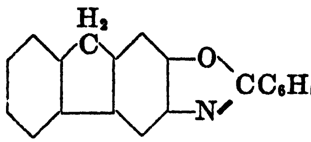
Derivatives of benzoxazole were reported by Bywater and co-workers (1) to possess anticonvulsant properties. In the hope that fluorene derivatives might have similar properties and less toxicity we undertook the present work.

Two new oxazoles, (I and II), were obtained by condensing 3-amino-2-hydroxyfluorene with phenylacetonitrile and with benzonitrile.



I

2-benzyl-9*H*-fluoreno [3,2] oxazole



II

2-phenyl-9*H*-fluoreno [3,2] oxazole

The low-boiling compounds, acetonitrile and acrylonitrile failed to react under the conditions employed. Dicyandiamide gave only intractable tars when heated with 3-amino-2-hydroxyfluorene.

The yield of the intermediate, 2-hydroxyfluorene, was considerably improved by hydrolyzing the diazonium chloride in a very dilute solution of sulfuric acid. Nitration of 2-hydroxyfluorene could give either the 1-nitro- or the 3-nitro-2-hydroxyfluorene. Other positions are eliminated by the subsequent formation of the oxazole ring. Previous workers (2) have shown that the nitration of 2-acetylaminofluorene gives, after hydrolysis, 2-amino-3-nitrofluorene. This was proved by the removal of the original 2-amino group and the conversion of the resulting nitro compound to the known 3-hydroxyfluorenone.

Ruiz (3) nitrated 2-methoxyfluorene and by heating the resulting compound in a sealed tube with ammonia obtained the identical 2-amino-3-nitrofluorene of Eckert and Langecker and of Bardout (2).

We have, therefore, assigned the 3-position to the nitro group in the compound obtained by the nitration of 2-hydroxyfluorene.

In an earlier paper Ruiz (4) reported the isolation of 3-acetylamino-2-hydroxyfluorene which he described as melting at 215° and which on analysis gave 5.48% nitrogen.

In the present work we heated 3-amino-2-hydroxyfluorene with acetic anhydride and also obtained a compound melting at 214–215°. This compound, however, contained 5.05% nitrogen and gave no reaction for a free phenolic group. A recalculation of the theoretical percentage of nitrogen for the *diacetyl* derivative gives 4.98%, not as Ruiz reports it 5.12%. This compound, m.p. 215°, is, therefore, 3-acetylamino-2-acetoxyfluorene.

On pouring the supernatent acetic anhydride solution into water we obtained a compound melting at 163° which gave 5.90% nitrogen and proved to be the 3-acetylamino-2-hydroxyfluorene (Calc'd: N, 5.86.) not previously isolated.

EXPERIMENTAL

2-Nitrofluorene and 2-aminofluorene were prepared by the method given in Organic Syntheses (5) as modified by Reid and Sampey (6).

2-Hydroxyfluorene. The method of Ruiz (4) modified as follows was employed. 2-Aminofluorene (25 g., 0.14 mole) was boiled in 900 cc. of water containing 33 cc. of concentrated hydrochloric acid until solution resulted. This was cooled quickly to 40° and a solution of 11 g. of sodium nitrite in 60 cc. of water was added with stirring. The resulting diazonium solution was slowly added (1 hour) to 2500 cc. of boiling water containing 41 cc. of concentrated sulfuric acid. On cooling, a mixture of white and dark-colored crystals separated. This was dissolved in 1250 cc. of warm 10% potassium hydroxide, filtered and acidified; yield 90%; a light cream-colored solid, m.p. 166–168°. Recrystallization from 80% alcohol gave white platelets, m.p. 169–171°. Diels (7) reports 171°.

3-Nitro-3-hydroxyfluorene. 2-Hydroxyfluorene (12 g., 0.07 mole) in 300 cc. of glacial acetic acid was slowly nitrated with 4.2 cc. of concentrated nitric acid mixed with an equal volume of water. The mixture was heated on the water-bath for 0.5 hours to complete the reaction and then was poured into 1200 cc. of ice water. A yellow solid melting at 141–146° was obtained in 95% yield. Ruiz (4) reports m.p. 145.6°. The chief contaminant was a dinitro compound. By treating 10 g. with 1000 cc. of boiling 94% ethanol the dinitro compound remained undissolved and was removed by filtration.

3-Amino-2-hydroxyfluorene. The filtrate obtained above was treated with 50 g. of sodium hydrosulfite in 200 cc. of water and boiled for 4 hours. About half the alcohol was distilled off and 7 g. of tan material melting with decomposition at 244° was obtained. Ruiz (4) reports 246° dec.

3-Acetylamino-2-acetoxyfluorene. To 2 g. of 3-amino-2-hydroxyfluorene in 10 cc. of glacial acetic acid was added 1.6 cc. of acetic anhydride. After refluxing for 2 hours it was allowed to cool and the precipitate was recrystallized twice from absolute alcohol with Darco. Four-tenths gram of fine white needles was obtained, m.p. 214–215°. This is the value given by Ruiz (4) but he mistakenly describes this substance as the monoacetylated compound, *q.v.*

Anal. Calc'd for $C_{17}H_{15}NO_3$: N, 4.98. Found N, 5.04.

3-Acetylamino-2-hydroxyfluorene. As the yield in the preceding experiment was unusually small the filtrate from the reaction was poured into water. There was obtained 0.7 g. of thicker flat needles which, when recrystallized from alcohol, melted at 163°.

Anal. Calc'd for $C_{15}H_{13}NO_2$: N, 5.86. Found: N, 5.90.

2-Benzyl-9H-fluoreno[3,2]oxazole. 3-Amino-2-hydroxyfluorene, 2 g. or 0.01 mole, was refluxed with 20 cc. of phenylacetonitrile at 229° for 5.5 hours. The mixture first turned black but eventually became red-brown as ammonia was evolved. On standing overnight light yellow needles formed; yield 1 g. (33%), m.p. 176–180°. The yellow material was washed with alkali and with water, dried and recrystallized twice from absolute alcohol with Darco. Colorless needles, m.p. 187°, were obtained. They were insoluble in hot and in cold water, slightly soluble in cold and very soluble in hot absolute alcohol; slightly soluble in cold ligroin (b.p. 90–120°) and somewhat soluble in hot; soluble in cold benzene, acetone, and ether and insoluble in alkali and acid.

Anal. Calc'd for $C_{21}H_{15}NO$: N, 4.71. Found: N, 4.68, 4.85.

2-Phenyl-9H-fluoreno[3,2]oxazole. 3-Amino-2-hydroxyfluorene, 2 g. or 0.01 mole, was boiled with 40 cc. of benzonitrile for 15 hours. This mixture also turned black and then gradually became red-brown. On cooling, 2.2 g. of light tan needles were obtained. After recrystallization from absolute alcohol with Darco, fine light yellow needles were obtained, melting at 184–185°.

The compound was insoluble in hot and in cold water, somewhat soluble in cold ethanol and very soluble in hot ethanol, more soluble in isoamyl alcohol. It was also soluble in cold methanol, benzene, acetone, and glacial acetic acid.

Anal. Calc'd for $C_{20}H_{13}NO$: N, 4.95. Found: N, 4.87, 4.85.

SUMMARY

Two new oxazoles derived from fluorene, 2-phenyl-9*H*-fluoreno[3,2]oxazole and 2-benzyl-9*H*-fluoreno[3,2]oxazole, have been prepared and characterized.

3-Acetylamino-2-hydroxyfluorene has been prepared and found to melt at 163° instead of 215° as previously reported. The compound melting at 215° has been shown to be 3-acetylamino-2-acetoxyfluorene.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PRINCETON UNIVERSITY]

A CONTRIBUTION TO THE STRUCTURE OF CITRININ

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Received December 13, 1948

The antibiotic, citrinin, is a metabolic product of various species of molds (*Penicillium citrinin* Thom, *Aspergillus candidus*). A structure for this substance was first proposed by Coyne, Raistrick and Robinson (1); however, subsequent investigations (2, 3) yielded evidence that that structure was incorrect. It was therefore of interest to reopen the subject with a view of arriving at a more suitable formulation. Three other groups of workers (4, 5, 6) have also engaged in this reinvestigation and their conclusions have appeared in recent publications. What follows constitutes the contribution of the present writers to this problem.

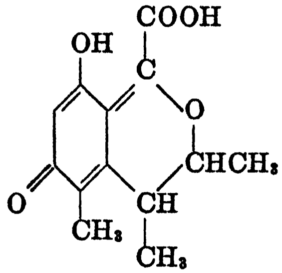
Citrinin (I, $C_{13}H_{14}O_5$) upon acid hydrolysis yields two isomeric substances, IIA and IIB, of the formula $C_{11}H_{16}O_3$. Hetherington and Raistrick (7) assumed IIB to be the optically inactive stereoisomer of IIA. Alkali fusion of IIA produces III, ($C_9H_{12}O_2$), which Cram (4) has shown to be identical with 4-methyl-5-ethylresorcinol by synthesis of that compound. At the time of publication of Cram's work we were engaged in the synthesis of 4-methyl-5-ethylresorcinol by a different route and we concur with Cram that III is identical with that synthetic substance. We have also synthesized 4-methyl-3,5-dihydroxyacetophenone in a manner which parallels our synthesis of 4-methyl-5-ethylresorcinol.

Cram proposed for the structure of IIA that of 4-methyl-5-(1-methyl-2-hydroxy)-propylresorcinol on the basis of a terminal methyl analysis of that substance indicative of three methyl groups, and on its reported coupling (2) with two moles of 2-methoxy-5-nitrobenzenediazonium chloride. This structure has two centers of asymmetry and consequently two pairs of racemates should be possible. Since only one racemate, IIB, has been reported, we undertook a further investigation of IIA and IIB. We have found that under the conditions of the acid hydrolysis of citrinin, IIA can be converted to IIB in seventy per cent yield. From the residual syrup we were unable to isolate any other substance. That IIB is actually a racemic compound of IIA and its optical antipode was shown by the partial resolution of its triacetylated derivative by the method of inoculation. Hetherington, *et al.* (7), reported that acetylation of IIA with acetic anhydride and pyridine yielded only a diacetate, while with acetic anhydride and sodium acetate they obtained the triacetate. We found that a triacetate of IIA (m.p. 88.2–89.5°, $[\alpha]_D$ +10.4°) was readily obtained with acetic anhydride and pyridine.

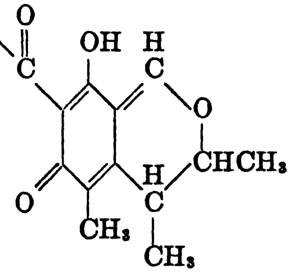
Confirmatory evidence that IIA has two free nuclear positions *ortho* and *para* to the phenolic hydroxyl groups as reported by Gore, *et al.* (2), was obtained by treatment of that substance with bromine water which yielded a dibromo derivative. Citrinin yields a positive test in the iodoform reaction. That the functional group responsible for this is retained in the dimethylated derivative of

IIA, ($[\alpha]_D$ −40.5°), was shown by subjecting that substance to Fuson and Tullock's (8) modification of the iodoform reaction which yielded a small but definite quantity of iodoform. Though our efforts to isolate the acid moiety from this reaction were inconclusive, a colored oil exhibiting a pronounced positive rotation was obtained. Conclusive proof of Cram's proposed structure for IIA was provided by subjecting levorotatory dimethyl IIA to the Oppenauer oxidation with aluminum isopropoxide. A dextrorotatory ketone was obtained as a colorless oil and was converted to its optically active semicarbazone derivative.

On the basis of this and other evidence we can assume with Gore, *et al.* (5) that the structure of citrinin can be represented by I, or if we assume that citrinin can couple with diazonium salts on an active C—H, formula IA is possible.



I



Ia

EXPERIMENTAL

2-Methyl-3,5-dinitrobenzoyl chloride. To 113 g. of 2-methyl-3,5-dinitrobenzoic acid (m.p. 207.5–208°) was added 105 g. of phosphorus pentachloride and the mixture was shaken to insure homogeneity. When the initial vigor of the reaction had subsided, the reaction was completed by heating for 2.5 hours on a hot water-bath and the phosphorus oxychloride was removed under reduced pressure over the course of three hours. Upon cooling, the material solidified to a cream-colored mass. This was purified by evaporation onto a cold finger in high vacuum at 80–90° to yield 108.5 g. (88.7%) of almost colorless crystals. Upon recrystallization from absolute ether tiny white needles, m.p. 63.5–64.0°, were obtained.

Anal. Calc'd for $C_8H_5ClN_2O_5$: C, 39.26; H, 2.10.

Found: C, 39.33; H, 2.15.

4-Methyl-3,5-dinitrobenzoyl chloride. When 113 g. of 4-methyl-3,5-dinitrobenzoic acid (m.p. 161.2–162.0°) was reacted with phosphorus pentachloride in the same manner used on the isomeric acid, a yield of 112.2 g. (91.6%) of the acyl chloride was obtained, which crystallized as colorless rhombs; m.p. 56.5–57.0°.

Anal. Calc'd for $C_8H_5ClN_2O_5$: C, 39.26; H, 2.10.

Found: C, 39.14; H, 2.08.

Ethyl 2-methyl-3,5-dinitrobenzoylacetoacetate. A solution of sodium ethoxide was prepared by treating 12 g. (0.52 atom) of freshly cut sodium with 150 cc. of absolute ethanol. The reaction was completed by heating the mixture on a steam-bath and then sufficient absolute ethanol was added to bring the volume of the solution up to 200 cc. Meanwhile 61 g. (0.25 mole) of 2-methyl-3,5-dinitrobenzoyl chloride was dissolved in sufficient absolute ether to give a volume of 1200 cc. In a three-necked flask, immersed in an ice-water bath and fitted with a mechanical stirrer and two dropping funnels, was placed 34 g. (0.261 mole) of ethyl acetoacetate. From one of the funnels 100 cc. of the sodium ethoxide solution was introduced into the flask and after fifteen minutes, 600 cc. of the benzoyl chloride solution was added slowly in a thin stream. The solution was allowed to react for an hour, stirring

being continuously maintained, and then a second portion of 50 cc. of sodium ethoxide solution was added, followed by a second portion of 300 cc. of the benzoyl chloride solution. In this portion-wise manner the entire quantities of the two reagents were combined with the acetoacetic ester, one hour being allowed to pass between the addition of one pair of the reagents and the subsequent addition of the following pair. The various portions used were:

Sodium Ethoxide cc.	*2-Methyl-3,5-dinitrobenzoyl Chloride* cc.
100.00	600.0
50.00	300.0
25.00	150.0
12.50	75.0
6.25	37.5
6.25	37.5

When the last portion had been added, the mixture was allowed to stand for 48 hours in a cold water bath. The precipitated product was collected by filtration, washed several times with ether, and dissolved in 10 l. of cold water and filtered from any insoluble material. Dissolution was slow and was aided by stirring. The filtrate was acidified with 1 *N* sulfuric acid and a precipitate was formed upon standing. The product was purified by recrystallization from methanol to yield 72.6 g. (85.9%) of pale flesh-colored prisms; m.p. 95–96°.

Anal. Calc'd for $C_{14}H_{14}N_2O_8$: C, 49.71; H, 4.17.
Found: C, 49.74; H, 4.09.

Ethyl 4-methyl-3,5-dinitrobenzoylacetoacetate. When 34 g. of ethyl acetoacetate was benzoylated with 61 g. of 4-methyl-3,5-dinitrobenzoyl chloride in the method detailed above, a yield of 73.7 g. (87%) of ethyl 4-methyl-3,5-dinitrobenzoylacetoacetate was obtained, crystallizing as almost colorless tiny needles; m.p. 81.0–81.5°.

Anal. Calc'd for $C_{14}H_{14}N_2O_8$: C, 49.71; H, 4.17.
Found: C, 50.06; H, 4.35.

2-Methyl-3,5-dinitroacetophenone and 2-methyl-3,5-dinitrobenzoylacetone. A mixture of 84.5 g. of ethyl 2-methyl-3,5-dinitrobenzoylacetoacetate and 8.5 liters of 40% sulfuric acid was refluxed with continuous stirring for eighteen hours. It is important that the stirrer employed be particularly effective so as to keep the oil suspended in the aqueous phase as fine droplets. Upon cooling the oil solidified and was collected. This product was triturated repeatedly with 2% sodium hydroxide until the decanted alkaline solution was colorless. The red-colored alkaline extract was immediately acidified with dilute sulfuric acid to precipitate the crude 2-methyl-3,5-dinitrobenzoylacetone, while the alkali insoluble acetophenone derivative was freed from remaining traces of 2-methyl-3,5-dinitrobenzoylacetone by dissolving it in ether and washing the ether solution with 2% sodium hydroxide. Evaporation of the ether solution yielded the crude 2-methyl-3,5-dinitroacetophenone which was purified by recrystallization from alcohol. The yield of this product was 82%. Further purification from petroleum ether, in which it was difficultly soluble, gave colorless needles melting at 71.5–72.5°.

Anal. Calc'd for $C_9H_8N_2O_5$: C, 48.67; H, 3.59.
Found: C, 48.59; H, 3.88.

The 2-methyl-3,5-dinitrobenzoylacetone was purified by two recrystallizations from 95% ethanol to yield 5.3 g. (8.1%) of colorless, long fine needles; m.p. 90.0–90.5°.

Anal. Calc'd for $C_{11}H_{10}N_2O_6$: C, 49.62; H, 3.78.
Found: C, 50.05; H, 3.92.

4-Methyl-3,5-dinitroacetophenone and 4-methyl-3,5-dinitrobenzoylacetone. Under the conditions of hydrolysis employed upon ethyl 2-methyl-3,5-dinitrobenzoylacetoacetate, 84.5 g. of ethyl 4-methyl-3,5-dinitrobenzoylacetoacetate yielded 44.8 g. (84.2%) of 4-methyl-3,5-dinitroacetophenone; m.p. 68–69°.

Anal. Calc'd for $C_9H_8N_2O_5$: C, 48.67; H, 3.59.
Found: C, 48.72; H, 3.28.

The yield of 4-methyl-3,5-dinitrobenzoylacetone was 3.5 g. (5.3%), which crystallized as very pale flesh-colored needles; m.p. 144.0–144.5°.

Anal. Calc'd for $C_{11}H_{10}N_2O_6$: C, 49.62; H, 3.78.
Found: C, 49.41; H, 3.65.

2-Methyl-3-nitro-5-aminoacetophenone and 2-methyl-3-amino-5-nitroacetophenone. A solution of 67 g. (0.35 mole) of anhydrous stannous chloride in 470 cc. of absolute methanol was saturated with dry hydrogen chloride while being chilled in a salt-ice bath. This solution was then slowly added, accompanied by stirring, to a solution of 26.43 g. (0.118 mole) of 2-methyl-3,5-dinitroacetophenone in 2 liters of absolute methanol, the temperature of which was maintained below 5°. After standing over night and allowing it to come to room temperature, the solution was slowly warmed in a water-bath and then refluxed for one-half hour. The clear light-yellow solution was concentrated to about 100 cc. under reduced pressure and then poured into a liter of water which produced a turbidity. This was exhaustively extracted with ether and the aqueous solution set aside for later treatment. After drying the ether extract with potassium carbonate, hydrogen chloride was passed in to precipitate the amine hydrochloride which was collected by filtration. The ether mother liquor was washed with water and then with sodium carbonate solution. Evaporation to dryness of this ether solution left a solid residue which was recrystallized from methanol to yield 5.9 g. (0.026 mole) of unchanged starting material. The amine hydrochloride was added to 300 cc. of water, whereupon the free base immediately separated. This was recrystallized from 95% ethanol to yield coral-colored crystals, presumably the alcoholate, which became bright yellow upon drying in a vacuum desiccator over sulfuric acid. Yield, 9.25 g. (51.8%) of product; m.p. 110.5–111.0°.

Anal. Calc'd for $C_9H_{10}N_2O_3$: C, 55.65; H, 5.19.
Found: C, 55.38; H, 4.98.

The aqueous solution, from which the preceding ether extract had been obtained, was heated to 90° and hydrogen sulfide passed in until the tin had been completely precipitated. After filtering off the stannic sulfide, the solution was made basic with 10% sodium hydroxide and extracted with ether. The ether extract was dried with potassium carbonate and then treated with hydrogen chloride to precipitate the amine hydrochloride. This was collected and added to 20 cc. of water whereupon the free base precipitated. Recrystallization from ethanol yielded 0.85 g. (4.8%) of tiny, bright yellow needles melting at 116.0–117.5°.

Anal. Calc'd for $C_9H_{10}N_2O_3$: C, 55.65; H, 5.19.
Found: C, 55.42; H, 5.44.

The two products are therefore the isomeric *2-methyl-3-nitro-5-aminoacetophenone* and *2-methyl-3-amino-5-nitroacetophenone*, although their particular identity has not been ascertained.

4-Methyl-3-nitro-5-aminoacetophenone. Reduction of 15.9 g. of 4-methyl-3,5-dinitroacetophenone with 40.4 g. of anhydrous stannous chloride as detailed above yielded 3.1 g. of the unreacted dinitroacetophenone and 6.2 g. (56%) of 4-methyl-3-nitro-5-aminoacetophenone as tiny orange needles melting at 158–159°.

Anal. Calc'd for $C_9H_{10}N_2O_3$: C, 55.65; H, 5.19.
Found: C, 55.47; H, 5.09.

2-Methyl-(3 or 5)-hydroxy-(5 or 3)-nitroacetophenone. To a suspension of 2.3 g. of the hydrochloride of 2-methyl-(3 or 5)-amino-(5 or 3)-nitroacetophenone (m.p. 110.5–111.0°) in 7.5 cc. of concentrated hydrochloric acid maintained at 0° there was slowly added 0.7 g. of finely powdered sodium nitrite accompanied by stirring. When the addition was complete, sufficient ice was added to give a volume of 25 cc. and then the clear yellow solution was poured into 160 cc. of 50% sulfuric acid and the solution warmed to 85° over the course of twenty-five minutes. After 1.5 hours at 85–90° the evolution of nitrogen was completed and the turbid yellow solution was cooled in an ice bath and extracted with ether. The

ether extract was evaporated to dryness and the residue crystallized from water and then benzene, in which it was difficultly soluble to yield 1.26 g. (60.3%) of colorless needles; m.p. 110.5–112°.

Anal. Calc'd for $C_9H_9NO_4$: C, 55.38; H, 4.64.

Found: C, 55.52; H, 4.48.

4-Methyl-3-nitro-5-hydroxyacetophenone. The same method of diazotization and hydrolysis was used upon 2.3 g. of the hydrochloride of 4-methyl-3-nitro-5-aminoacetophenone. A yield of 1.3 g. (62%) of the 4-methyl-3-nitro-5-hydroxyacetophenone was obtained as almost colorless needles; m.p. 152.5–153.5°.

Anal. Calc'd for $C_9H_9NO_4$: C, 55.38; H, 4.64.

Found: C, 55.17; H, 4.48.

2-Methyl-(3 or 5)-hydroxy-(5 or 3)-aminoacetophenone hydrochloride. Granular tin (14.23 g.) was divided into ten approximately equal portions and likewise 6.85 g. of 2-methyl-(3 or 5)-hydroxy-(5 or 3)-nitroacetophenone was divided into ten portions. To 85 cc. of 25% hydrochloric acid heated under reflux on a steam-bath was added one portion of the tin followed by a portion of acetophenone derivative. When the latter had dissolved completely, another portion of the tin and of the nitroacetophenone were added. After five portions of each of the reagents had been added in this manner, an additional 10 cc. of hydrochloric acid was added and the portionwise addition of the reagents continued. To complete the reaction, 8 g. of tin and 16 cc. of the acid were added and the mixture refluxed 3 hours longer. The solution was decanted from the unreacted tin and diluted to 1200 cc. with hot water and the tin precipitated with hydrogen sulfide. After removal of the tin sulfide, the filtrate was evaporated to dryness under reduced pressure in an atmosphere of nitrogen to yield 6.3 g. of white needles. Upon standing in air, the product took on a tannish tinge and efforts to isolate the free base indicated that that substance was unstable, so it was employed in the subsequent diazotization without further purification.

4-Methyl-3-amino-5-hydroxyacetophenone hydrochloride. By the same method of reduction, 3.1 g. of 4-methyl-3-nitro-5-hydroxyacetophenone yielded 2.8 g. of the crude hydrochloride of 4-methyl-3-amino-5-hydroxyacetophenone. Like its 2-methyl isomer, the free base is apparently unstable.

2-Methyl-3,5-dihydroxyacetophenone. To 12.5 cc. of concentrated hydrochloric acid was added 1.01 g. of the unpurified hydrochloride of 2-methyl-(3 or 5)-hydroxy-(5 or 3)-aminoacetophenone and the solution warmed to expel the hydrogen chloride which appears to have an adverse effect on the reaction. The solution was diluted with 100 cc. of cold water, cooled to 0° in an ice-bath, and then potassium nitrite solution (0.5 g. in 20 cc. of water) was introduced beneath the surface accompanied by stirring until the first permanent indication of excess nitrous acid. This required about 17 cc. of the nitrite solution. The clear diazonium solution was slowly warmed in a water-bath to 60° and maintained there for fifty minutes. The warm solution was filtered from a small amount of tar, cooled, and extracted with ether. Evaporation of the ether left a light-red oil which was dissolved in hot benzene, in which it was difficultly soluble, and refluxed with Darco. After filtering off the Darco and cooling, tan needles separated. Further purification was accomplished by dissolution in absolute ether, filtration through activated alumina, and then evaporation of the colorless filtrate to dryness. A final recrystallization from benzene yielded 0.42 g. (51%) of colorless platelets, m.p. 160.5–161.2°.

Anal. Calc'd for $C_9H_{10}O_3$: C, 65.04; H, 6.06.

Found: C, 65.02; H, 6.10.

4-Methyl-3,5-dihydroxyacetophenone. When 1.68 g. of the hydrochloride of 4-methyl-3-amino-5-hydroxyacetophenone was diazotized and hydrolyzed by the preceding method, 0.59 g. (43%) of faintly colored platelets melting at 190–191° were obtained.

Anal. Calc'd for $C_9H_{10}O_3$: C, 65.04; H, 6.06.

Found: C, 64.59; H, 5.91.

The attempted Clemmensen reduction of this compound to the desired 2-methyl-5-ethylresorcinol was unsuccessful.

4-Methyl-5-ethylresorcinol. A mixture of 10 cc. of 12% hydrochloric acid and 4.5 g. of amalgamated mossy zinc was heated under reflux on a steam-bath and 0.5 g. of 2-methyl-3,5-dihydroxyacetophenone was added in small portions over the course of 45 minutes. A quantity of tarry material was formed and floated on the surface during this period. The mixture was then refluxed for seven hours, 0.3 cc. of concentrated hydrochloric acid being added at the end of each hour. The hot solution was filtered from the tarry material and the unreacted amalgam and allowed to stand overnight, whereupon a quantity of colorless crystals separated. These were recrystallized from hot water and found to melt at 68–69°. When mixed with the monohydrate of substance III obtained by the degradation of citrinin (m.p. 68–69°), there was no depression of the melting point. Sublimation of the monohydrate of the synthetic 4-methyl-5-ethylresorcinol in high vacuum at 85° yielded the anhydrous form melting at 93–94°. When mixed with substance III, which we have found to melt at 93.4–94.2° although in the literature (7, 2) it is reported to melt at 97–99° and 98–99°, there was no depression of the melting point; hence these two substances are identical. The yield of the synthetic 4-methyl-5-ethylresorcinol was 0.21 g. (46%).

Anal. Calc'd for $C_9H_{12}O_2$: C, 71.02; H, 7.94.
Found: C, 71.10; H, 7.67.
Calc'd for $C_9H_{12}O_2 \cdot H_2O$: C, 63.51; H, 8.29.
Found: C, 63.63; H, 8.21.

Racemization of substance IIA. A solution of 0.5 g. of substance *IIA* (m.p. 127–128°; $[\alpha]_D$ −43.4° in methanol) in 20 cc. of 2 *N* sulfuric acid was refluxed for nineteen hours, at the end of which the solution was optically inactive. The mixture was allowed to cool and then filtered through a layer of Darco. The filtrate was extracted with ether and the ether extract, after drying with magnesium sulfate, was evaporated to dryness to leave a residual yellow oil. This was crystallized from 25 cc. of hot chloroform and twice from water to yield 0.35 g. (70%) of colorless, optically inactive crystals melting at 169–170°. A mixed melting point with substance IIB (m.p. 169–170°), obtained by the acid hydrolysis of citrinin, gave no depression of the melting point.

Triacetylation of substance IIA. To a mixture of 15 cc. of acetic anhydride and 4 cc. of pyridine was added 1.96 g. of substance IIA. After standing over night at room temperature, the solution was warmed to 75° for one hour and then evaporated under reduced pressure to leave a colorless syrup. This syrup was crystallized from 40% methanol to yield 2.9 g. (90%) of the triacetylated derivative, m.p. 88.2–89.5°, $[\alpha]_D^{20}$ + 10.8° in methanol.

Anal. Calc'd for $C_{17}H_{22}O_6$: C, 63.34; H, 6.87.
Found: C, 63.25; H, 6.70.

Hydrolysis of this product with 2 *N* sulfuric acid yielded the optically active starting material.

Triacetylation of substance IIB and partial resolution of the acetylated derivative into its enantiomorphic components. Using the same method of acetylation on 0.95 g. of substance IIB a colorless, optically inactive syrup was obtained. This syrup was dissolved in 10–15 cc. of methanol and water was added until a slight permanent turbidity was produced which dissolved upon warming. The solution was allowed to cool to room temperature and then innoculated with the merest trace of optically active IIA triacetate. An hour or so later it was observed that a quantity of colorless, transparent platelets had separated. These were collected and the mother liquor set aside. These platelets melted at 83–83.5° and after a second recrystallization at 85.5–87.0°. They were optically active, $[\alpha]_D^{20}$ + 9.6°, and of the correct melting point.

Anal. Calc'd for $C_{17}H_{22}O_6$: C, 63.34; H, 6.87.
Found: C, 63.14; H, 6.84.

Meanwhile from the original mother liquor an additional crop of crystals had separated. These were of two sorts—one variety was in the form of clusters of small, rather chunky plates, the other consisted of four unusually large and well formed thin square plates. The two types were separated manually. The large plates melted at 83–85° and when admixed

with IIA triacetate gave a pronounced depression of the melting point. A second crystallization from 50% ethanol raised the melting point to 85–86.5°. The product was optically active with $[\alpha]_D^{20}$ −9.4° in methanol.

Anal. Calc'd for $C_{17}H_{22}O_6$: C, 63.34; H, 6.87.

Found: C, 63.33; H, 6.67.

The clusters of small chunky platelets melted at 64–69° and admixture with IIA triacetate resulted in an increase in the melting point.

Iodoform reaction of dimethylated substance IIA. Substance IIA was methylated by the method of Hetherington and Raistrick (7). This (0.45 g.), an optically active oil ($[\alpha]_D^{20}$ −40.5°), was dissolved in 35 cc. of pure dioxane and then 5 cc. of 10% sodium hydroxide was added and the mixture thoroughly shaken. To this was then added 18 cc. of an iodine-potassium iodide solution (50 g. of iodine and 25 g. of potassium iodide dissolved in water up to 200 cc.). After shaking for five minutes at room temperature, the reaction mixture was warmed for two minutes in a water-bath at 60°, whereupon the solution became quite light in color. An additional 3 cc. of the sodium hydroxide solution was added and the mixture shaken and poured into 250 cc. of cold water which caused the formation of a small quantity of precipitate. This was collected by filtration and smelled strongly of iodoform. Steam distillation of this gummy product yielded a small but definite quantity of iodoform melting at 117–119°.

Dibromo derivative of substance IIA. A solution of 0.2 g. of substance IIA in 60 cc. of water was treated with an equal volume of freshly prepared bromine water. The bromine water was added in small portions accompanied by swirling during the course of 10 minutes. A turbid solution resulted which was clarified by the addition of 15 cc. of sodium bisulfite solution. The mixture was then extracted with ether, the ether extract dried with magnesium sulfate and filtered through a layer of activated alumina. After concentrating the ether solution to 5 cc., it was diluted with 15 cc. of petroleum ether and the mixture further concentrated on a steam-bath until the first indication of an oily precipitate was observed. Upon cooling a crystalline solid separated which was recrystallized twice from hot water to yield flat, colorless needles melting at 129–129.5°. Admixture of this substance with the starting material gave a pronounced depression of the melting point.

Anal. Calc'd for $C_{11}H_{14}Br_2O_3$: C, 37.29; H, 3.98.

Found: C, 37.44; H, 3.86.

Oppenauer oxidation of dimethylated substance IIA. To a mixture of 36 cc. of benzene and 12 cc. of acetone were added 1.97 g. (8 mmole) of dimethyl IIA ($[\alpha]_D$ −40.5°) and 1.62 g. (8 mmole) of aluminum isopropoxide. The solution was refluxed for 21.5 hours whereupon an additional 5 cc. of acetone was added and refluxing continued for another 3.5 hours. After cooling, this solution was washed twice with dilute hydrochloric acid and then dried with sodium sulfate. Filtration through a layer of activated alumina and Darco, followed by evaporation left 1.84 g. of a brown oil. This was purified by distillation in high vacuum in a molecular still. A pale-yellow oil came over between 48–55° at a pressure of 10^{-4} mm. This was optically active with $[\alpha]_D$ +45.0° in methanol, and $[\alpha]_D$ +38.5° in chloroform.

Anal. Calc'd for $C_{13}H_{18}O_3$: C, 70.25; H, 8.16.

Found: C, 69.41; H, 8.33.

Semicarbazone of the ketone obtained by the oxidation of dimethyl substance IIA. To a solution of 0.5 g. of the ketone obtained above dissolved in 10 cc. of ethanol was added a solution of 1 g. of semicarbazide hydrochloride and 1.5 g. of sodium acetate in 5 cc. of water. The mixture was refluxed for two hours and the alcohol then removed by distillation. Upon dilution with water and chilling in an ice-bath, a white solid precipitated. This was collected, dissolved in chloroform, filtered through a layer of alumina and then diluted with ether, whereupon the semicarbazone precipitated. The product melted to a clear, somewhat reddish liquid at 194.8°, with previous shrinking at 192°; $[\alpha]_D$ +43.8° in methaol.

Anal. Calc'd for $C_{14}H_{21}N_3O_3$: C, 60.19; H, 7.57.

Found: C, 60.25; H, 7.38.

SUMMARY

1. Additional evidence is presented for the structure of the antibiotic citrinin.

2. An alternative synthesis is described for 4-methyl-5-ethylresorcinol, and its identity with substance III, obtained by the degradation of citrinin, is shown, in agreement with Cram (4).

3. A parallel synthesis of 4-methyl-3,5-dihydroxyacetophenone is described.

PRINCETON, N. J.

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[CONTRIBUTION NO. 172 FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, FORDHAM UNIVERSITY]

STUDIES IN THE THIOPHENE SERIES. III. CONDENSATIONS OF THIOPHENEALDEHYDES[1]

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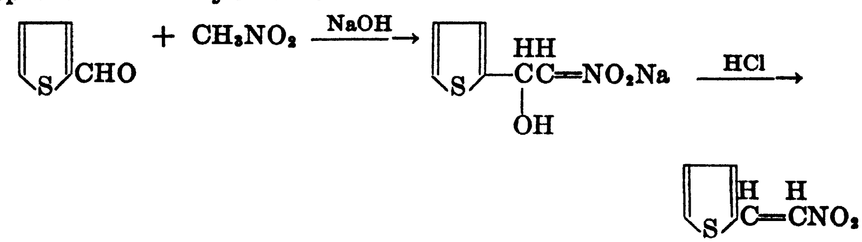
In continuation of studies in the thiophene series (1a, b) conducted in this laboratory, it was decided to apply some typical aromatic aldehyde condensations to thiophenealdehydes to determine the feasibility of these reactions and the effect of various substituent groups. The syntheses reported in this communication include condensations with nitromethane and nitroethane and subsequent dehydration of the nitro alcohol to yield unsaturated nitro compounds; the Perkin reaction (Doebner modification) to yield acrylic acids and the Claisen condensation to give acrylic esters. These reactions may be indicated for 2-thiophenecarboxaldehyde as follows:

(I)



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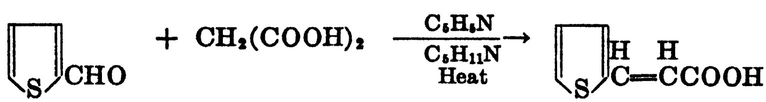

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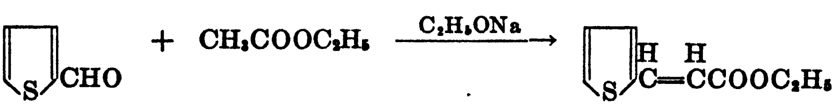
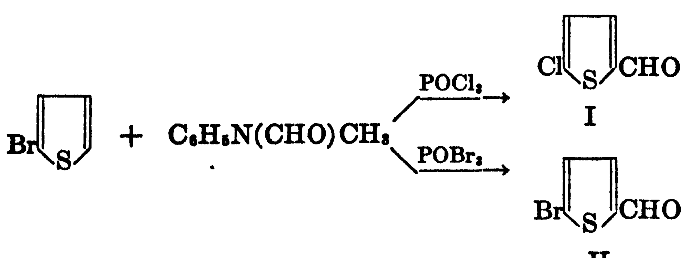


As mentioned in the first paper of this series, in using N-methylformanilide and phosphorus oxychloride for the preparation of thiophenealdehydes, it was found that starting with 2-bromothiophene a replacement of the bromine atom took place, yielding mainly 5-chloro-2-thiophenecarboxaldehyde (I). However, if phosphorus oxybromide was substituted for the oxychloride, it was possible to obtain 5-bromo-2-thiophenecarboxaldehyde (II) in yields of 50–55%:

(IV)



[1] This investigation was aided, in part, by a grant from the Office of Naval Research. The analyses were carried out by M. Bier of this Department.

In the condensations of the thiophenealdehydes with nitromethane, it was found that upon dehydration of the reaction products with hydrochloric acid the normal unsaturated nitro compounds were obtained. It has been previously reported (2) that the condensation of 2-thiophenecarboxaldehyde with nitromethane yielded a bright yellow volatile crystalline substance in 20% yield, which was considered to be the analog of ω-nitrostyrene. However, neither experimental details of the preparation nor an analysis of the compound were presented. By following the standard method (3) for the condensation of aldehydes and nitroparaffins, we obtained ω-nitro-2-vinylthiophene in 78% yield as well as various other substituted ω-nitrovinylthiophenes. It was also found possible to condense nitroethane with 2-thiophenecarboxaldehyde, but 1-nitropropane did not condense under the conditions employed, probably due to the lower reactivity of the active hydrogen in this compound. Table I summarizes the data available on these compounds.

TABLE I

CONDENSATION PRODUCTS OF THIOPHENEALDEHYDES AND NITROPARAFFINS

ALDEHYDE	CONDENSATION PRODUCT	YIELD, %	M.P., °C	ANAL.					
				Calc'd			Found		
				C	H	N	C	H	N
2-Thiophene carboxaldehyde	ω-Nitro-2-vinylthiophene	78	79–80[a]	46.44	3.25	9.03	46.62	3.28	8.89
2-Thiophene carboxaldehyde	1-(2-thienyl)-2-nitropropene	44	68.5	49.69	4.17	8.28	49.77	4.38	8.24
3-Methyl-2-thiophene carboxaldehyde	3-Methyl-ω-nitro-2-vinylthiophene	14	66–67	49.69	4.17	8.28	49.81	4.26	8.12
5-Methyl-2-thiophene carboxaldehyde	5-Methyl-ω-nitro-2-vinylthiophene	48	79–81	49.69	4.17	8.28	49.90	4.31	8.29
5-Ethyl-2-thiophene carboxaldehyde	5-Ethyl-ω-nitro-2-vinylthiophene	32	56–57[b]	52.44	4.95	7.65	52.70	5.23	7.85
5-Propyl-2-thiophene carboxaldehyde	5-Propyl-ω-nitro-2-vinylthiophene	26	36.5[b]	54.79	5.62	7.10	54.60	5.64	7.25
5-Chloro-2-thiophene carboxaldehyde	5-Chloro-ω-nitro-2-vinylthiophene	72	84.5–85	38.01	2.14	7.40	38.20	2.28	7.60
5-Bromo-2-thiophene carboxaldehyde	5-Bromo-ω-nitro-2-vinylthiophene	69	91–92	30.78	1.72	5.99	31.10	2.03	6.18

[a] Probably same compound reported in Ref. (2) in 20% yield; m.p. 79–83°.

[b] Obtained from reaction mixture as oils, which were taken up in alcohol and crystallised upon cooling.

The aldehyde-nitroparaffin condensation products listed in Table I were prepared by using dilute sodium hydroxide as the condensing agent. Previous

work from this laboratory (4) indicated that coordination compounds of the type $Mg[Al(OC_2H_5)_4]_2$ can be applied as catalytic agents in this type of condensation. While it was found that ω-nitrovinylthiophene could be obtained, the yields (20–30%) and the formation of tarry products lessen the effective use of this type of catalyst with thiophenealdehydes.

The yields reported in Table I indicate that the activity of the carbonyl group of the substituted thiophenealdehydes in this reaction is similar to the trends observed with substituted benzaldehydes (5). That is, a compound containing a halogen group in the *para* position will give approximately the same yield as the unsubstituted aldehyde, while a methyl group in any position will decrease the yield and this effect falls off in the order *ortho* > *para*. The lower yields obtained with the ethyl and propyl substituted aldehydes may be due to the fact that the resulting nitro compounds are low melting and are obtained as oils which crystallize with difficulty.

The Perkin reaction itself, using acetic anhydride and sodium acetate, does not work effectively with 2-thiophenecarboxaldehyde (6). However, the Doebner modification with malonic acid in pyridine solution gives excellent yields of 2-thienylacrylic acid (2). In applying this reaction to the substituted thiophenealdehydes, it was found that uniformly high yields of the corresponding acrylic acids in the range of 80–85% could be obtained.

The Claisen condensation utilizing sodium ethoxide and ethyl acetate to yield acrylic esters has not been previously applied to the thiophenealdehydes. Since in many cases in synthetic work it is advantageous to obtain the ester directly, it was deemed suitable to investigate this synthesis. It was found that it was better to run the reaction at a lower temperature than in the benzene series; for example at 0–5°, the yield of ethyl β-(2-thienyl)acrylate was 35%, while at −10 to −15° the yield was 49%. Table II summarizes the data on the acrylic acids and esters prepared.

The Claisen synthesis is not so successful as the Doebner modification, neither from the viewpoint of yields nor of convenience. Even when the temperature is kept at −10 to −15°, a rather large amount of tarry residue results from the Claisen condensation. The substituent groups apparently have no effect on the Doebner modification, while in the ester synthesis the maximum yields are obtained from the alkyl substituted aldehydes. In the case of the chloroaldehyde it was not found possible to obtain the acrylic ester directly, the main product being 5-chloro-2-thiophenecarboxylic acid.

In general, it appears that the reactions of the thiophenealdehydes are very similar to those exhibited by benzaldehydes and that the substituents exert a similar effect in both series. Previous workers have shown that thiophenealdehydes undergo such transformations as the simple and crossed Cannizzaro reactions (7), the Claisen-Schmidt condensation with ketones (8), and reactions with other compounds containing an active hydrogen atom such as hippuric acid and hydantoin (2). The benzoin condensation has also been applied to 2-thiophenecarboxaldehyde (1b). The reactions as covered in the present communication give further evidence that the thiophenealdehydes enter into the normal reactions characteristic of the aromatic aldehyde function.

TABLE II

Acrylic Acids and Esters from Thiophenealdehydes

Starting Aldehyde	Acrylic Acids						Acrylic Esters[d]							
	Yield %	M.P., °C	Anal.				Yield %	B.P., °C/mm.	d_4^{20}	n_D^{20}	Anal.			
			Calc'd		Found						Calc'd		Found	
			C	H	C	H					C	H	C	H
2-Thiophenecarboxaldehyde	85	143–144[a]	54.52	3.92	54.30	3.98	49	110–116/3.5	1.1439	1.5868	59.32	5.53	59.20	5.67
5-Methyl-2-thiophenecarboxaldehyde	82	165–166	57.12	4.79	57.20	4.75	55	116–122/5	1.1218	1.5834	61.19	6.16	61.26	6.21
3-Methyl-2-thiophenecarboxaldehyde	80	172–173	57.12	4.79	57.30	4.84	58	121–126/3	1.1365	1.5837	61.19	6.16	61.20	6.17
5-Ethyl-2-thiophenecarboxaldehyde	85	102–103	59.32	5.53	59.51	5.68	57	122–128/2	1.0968	1.5780	62.85	6.66	62.70	6.57
5-Propyl-2-thiophenecarboxaldehyde	83	109–110	61.19	6.17	61.13	6.23	63	135–140/2	1.0724	1.5708	64.24	7.14	64.23	7.28
5-Chloro-2-thiophenecarboxaldehyde	85	201–203d.[b]	44.52	2.67	44.70	2.80	[c]							

[a] Ref. (2) gives 143–144°.

[b] Darkens at 190°.

[c] Acrylic ester not isolated; main product is 5-chloro-2-thiophenecarboxylic acid.

[d] The acrylic esters were hydrolyzed by refluxing with 25% sodium hydroxide solution for three hours. Acidification and recrystallization of the product yielded the corresponding acrylic acids, confirmed in each case by a mixed m.p. with the acids obtained by the Doebner modification.

EXPERIMENTAL[2]

5-Bromo-2-thiophenecarboxaldehyde. In a round-bottom flask were placed 32.6 g. (0.2 mole) of 2-bromothiophene, 45 g. of N-methylformanilide (0.32 mole), and 95.5 g. (0.33 mole) of phosphorus oxybromide. Upon addition of the oxybromide, a vigorous reaction occurred. The reaction mixture was cooled until the evolution of hydrogen bromide had subsided and then heated on a steam-bath for an hour. Then cooling was again applied and the contents of the flask carefully neutralized with excess aqueous sodium acetate. The mixture was steam distilled, the distillate extracted with ether, the ether extract washed with 6 *N* hydrochloric acid and with 5% sodium bicarbonate solution, dried over sodium sulfate and rectified. There was obtained 20.5 g. (54%) of 5-bromo-2-thiophenecarboxaldehyde (9). B.p. 80–83/2 mm.

Semicarbazone, m.p. 200–201°.

Anal. Calc'd for $C_6H_6BrN_3OS$: N, 16.95. Found: N, 17.12.

Acid, m.p. 141–141.5°. Mixed m.p. with an authentic sample (10) showed no depression.

Anal. Calc'd for $C_5H_3BrO_2S$: C, 29.00, H, 1.46.

Found: C, 29.16, H, 1.60.

Condensations with nitroparaffins. The condensations with the nitroparaffins were run according to the method outlined in the literature. As an example, the reaction of 2-thiophenecarboxaldehyde with nitromethane is given.

ω-Nitro-2-vinylthiophene. 2-Thiophenecarboxaldehyde (37 g., 0.33 mole), nitromethane (20 g., 0.33 mole), and 75 cc. of methyl alcohol were mixed in a 3-neck flask fitted with a thermometer, a mechanical stirrer and a separatory funnel. The temperature was kept between 10–15°, while a solution of 14 g. of sodium hydroxide in 50 cc. of water was added slowly. A bulky precipitate formed during the addition of the alkali. After fifteen minutes standing, the pasty mass was converted to a clear solution by the addition of ice-water. This solution was added slowly to a hydrochloric acid solution (made by diluting 70 cc. of concentrated hydrochloric acid with 100 cc. of water). The yellow crystals so formed were recrystallized from an alcohol-water mixture with charcoal. There was obtained 40.5 g. (78%) of ω-nitro-2-vinylthiophene, yellow crystals, m.p. 79–80°.

The condensation utilizing magnesium aluminum ethoxide was run in the following manner: 2-Thiophenecarboxaldehyde (11.2 g., 0.1 mole), nitromethane (6 g., 0.1 mole), and 1 g. of magnesium aluminum ethoxide were placed in a flask in an ice-water bath. The flask was then stoppered and after two to three hours was removed from the ice-bath and allowed to stand twenty-four hours at room temperature. A large excess of hydrochloric acid was added and the mixture warmed on the steam-bath for twenty minutes. After ether extraction, drying and rectification, there was obtained 3.5 g. (23%) of ω-nitro-2-vinylthiophene, b.p. 155–170°/9 mm., which after recrystallization from an alcohol-water mixture had m.p. 79–80°.

Preparation of thienylacrylic acids. The method utilized was the same in all cases. As an example the preparation of 2-thienylacrylic acid is given.

2-Thienylacrylic acid. 2-Thiophenecarboxaldehyde (11.2 g., 0.1 mole), malonic acid (20.4 g., 0.2 mole), 50 cc. of dry pyridine, and 1 cc. of piperidine were heated on a steam-bath for two hours and then boiled for five minutes. After cooling, the solution was poured into water and treated with excess hydrochloric acid. Filtration and recrystallization from an alcohol-water mixture yielded 13.1 g. (85%) of 2-thienylacrylic acid, m.p. 143–144°.

Preparation of thienylacrylic esters. The procedure utilized was the same for all of the thiophene compounds and followed that given in the literature (11) with the exception that the temperature was kept at −10 to −15° during the addition of the thiophenealdehydes. The example presented outlines the basic procedure.

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[2] The nitroparaffins used in this work were obtained through the courtesy of the Commercial Solvents Corporation and the phosphorus oxybromide was placed at our disposal by the Dow Chemical Company.

Ethyl β-(2-thienyl)acrylate. Sodium (7.2 g., 0.31 mole) was prepared in a finely divided form by heating in dry xylene and stirring vigorously while the mixture cooled to room temperature. The xylene was decanted off and to the sodium was added absolute ethyl acetate (115 cc., 1.2 mole) and 1 cc. of absolute ethyl alcohol. The flask was quickly cooled to −10° and 28 g. (0.25 mole) of 2-thiophenecarboxaldehyde was added slowly from a separatory funnel with agitation. The temperature was kept between −10° to −15°. After addition of the aldehyde, the stirring was continued for one hour and the temperature allowed to rise to 0–5°. Then 25 cc. of glacial acetic acid was added and the mixture was carefully diluted with water. The ester layer was separated and the water layer extracted with 20–25 cc. of ethyl acetate. The combined ester layer was washed with 6 *N* hydrochloric acid and dried over sodium sulfate. Fractionation yielded 22.2 g. (49%) of ethyl β-(2-thienyl)acrylate. B.p. 110–116°/3.5 mm.

SUMMARY

1. Methods are presented for the condensation of some thiophenealdehydes with nitroparaffins, malonic acid and ethyl acetate. Physical properties of the products obtained are recorded.

2. The effects of some substituent groups in the above condensations are discussed.

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[Contribution from the Avery Laboratory, University of Nebraska]

ULTRAVIOLET ABSORPTION SPECTRA OF SOME AMINO-SUBSTITUTED UNSATURATED KETONES

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In a previous investigation (1) the absorption spectra of some amino-substituted α,β-unsaturated ketones and related compounds were measured between 310 and 700 mμ. In that paper a general discussion of the resonance possibilities in such structures and their relationships to the spectra was given. At that time it was stated that a more complete study of the ultraviolet absorption spectra of such compounds was being undertaken. The earlier study included derivatives of only one α,β-unsaturated ketone, namely, benzalacetophenone. It was of interest to extend the study to derivatives of other α,β-unsaturated ketones such as benzalacetone and ethylideneacetophenone to observe the effect on the spectra of the presence and location of the phenyl groups.

The compounds (I)–(XV) for this investigation were freshly prepared, either according to methods given in the literature or as indicated in the experimental section. No one had previously reported the preparation of an α-amino derivative of ethylideneacetophenone. α-Bromoethylideneacetophenone was prepared for the first time from the dibromide of ethylideneacetophenone (2) by a modification of the method previously described for α-bromobenzalacetone (3). Morpholine was then added to the α-bromoethylideneacetophenone to give the crude α-bromo-β-morpholinobutyrophenone. This latter product was treated with sodium ethoxide, in the manner previously described for preparing α-aminobenzalacetones (4), to give α-morpholinoethylideneacetophenone (VIII).

β-Morpholinobenzalacetone (XI) was prepared from phenylacetylacetylene by a method similar to that described by Andre (5) for related compounds.

EXPERIMENTAL[1]

α-Bromoethylideneacetophenone. A 30.0 g. sample of α,β-dibromobutyrophenone (2), m.p. 95–97°, and 9.0 g. of sodium acetate were mixed with 75 ml. of 95% alcohol. This mixture was refluxed for four hours. The cooled reaction mixture was filtered to remove the sodium bromide, and the solvent removed under reduced pressure. The product was extracted from the residue with ether. The ether solution was washed several times with saturated saltwater and twice with saturated, aqueous sodium bicarbonate solution. The ether solution was dried and evaporated. The residual semi-solid product was recrystallized from 95% alcohol to give 15 g. of colorless crystals, m.p. 70–71°.

Anal. Calc'd for $C_{10}H_9BrO$: C, 53.33; H, 4.03; Br, 35.51.

Found: C, 53.41; H, 4.27; Br, 35.54.

α-Morpholinoethylideneacetophenone, (VIII). A 10.0 g. sample of α-bromoethylideneacetophenone was dissolved in 30 ml. of a 50-50 dry ether-petroleum ether mixture. This solution was cooled to 0° and 5.0 g. of morpholine added. After standing in the ice-chest for twelve hours the waxy, precipitated material was removed, washed with water, dried

[1] The micro analyses for carbon, hydrogen, nitrogen and bromine were determined by the Clark Microanalytical Laboratories of Urbana, Illinois.

and recrystallized from petroleum ether to give 5.0 g. of the crude addition product, m.p. 85–91°. This slightly yellow product was added to a boiling solution of 0.48 g. of sodium in 12 ml. of absolute alcohol. The reaction mixture was cooled and cold water added to precipitate a brown solid. This crude product was recrystallized once from ether and once from alcohol and water to give 3.0 g. of pale-yellow crystals, m.p. 98–99°.

Anal. Calc'd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06.
Found: C, 72.61; H, 7.64; N, 6.02.

TABLE I

ULTRAVIOLET ABSORPTION MAXIMA AND MINIMA FOR α,β-UNSATURATED KETONES IN HEPTANE SOLUTION

COMPOUND	MAXIMA		MINIMA		REFERENCE TO PREP.
	λ mμ	ε × 10⁻³	λ mμ	ε × 10⁻³	
I Benzylacetophenone	238	12.4	260	1.10	(6)
	280	1.50			
II Benzalacetophenone	226	12.1	241	4.85	(7)
	299	23.9			
III Benzalacetone	224.5	11.2	223	10.8	(8)
	279	21.6	234	1.37	
IV Ethylideneacetophenone	250	17.5			(2)
V Benzalacetophenone, α-N-methylbenzylamino-	248	17.3	224	12.1	(4b)
	286	16.7	267	14.6	
	392	1.55	343	1.14	
VI Benzalacetophenone, α-morpholino-	249	16.7	225	10.6	(9)
	278	15.7	267	15.1	
	365	1.48	234	1.28	
VII Benzalacetone, α-morpholino-	267	8.57	242	7.56	(10)
VIII Ethylideneacetophenone, α-morpholino-	242	16.9	268	1.25	new
	282	1.50	299	0.64	
	329	0.97			
IX Benzalacetophenone, β-benzylamino-	241	13.7	225	11.1	(11)
	346	19.2	283	1.25	
X Benzalacetophenone, β-morpholino-	245	16.4	225	11.7	(9)
	328	13.0	284	3.44	
XI Benzalacetone, β-morpholino-	236	9.57	263	5.13	new
	295	10.5			
XII Ethylideneacetophenone, β-morpholino-	242	8.45	222	6.00	(10)
	320	17.3	268	1.40	
XIII Ethylideneacetone, β-amino-	285	6.12	225	0.19	(12)
XIV Benzalacetophenone, p-dimethylamino-	254	17.6	226	6.45	(13)
	385	33.3	297	1.82	
XV Benzalacetone, p-dimethylamino-	243	10.6	280	2.15	(14)
	360	29.4			

β-Morpholinobenzalacetone, (XI). A method similar to that reported by Andre (5) for such compounds was used here. Phenylacetylacetylene (0.8 g.) was dissolved in 5 ml. of ether and the solution cooled in an ice-bath. To this was added 0.8 g. of morpholine. The mixture was allowed to stand in the ice-chest for a week. The reaction mixture was diluted with ether, washed several times with water, dried and evaporated. The residual dark product was recrystallized from petroleum ether and from heptane to give 0.4 g. of colorless crystals, m.p. 83–85°.

Anal. Calc'd for $C_{14}H_{17}NO_2$: C, 72.71; H, 7.41; N, 6.05.
Found: C, 72.90; H, 7.25; N, 5.90.

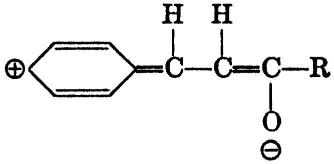
Absorption spectra measurements. These studies were made with highly purified (15) heptane-from-petroleum solutions of compounds (I)–(XV), using a model DU Beckman spectrophotometer. The relative transmission of our heptane when compared with distilled water was 72% at 220 mμ, 90% at 235 mμ and 100% at 265 mμ. Care was taken to avoid the exposure of the dilute solutions to sunlight and all measurements were made within two hours of their preparation from fresh materials.

The wave-length and molar extinction coefficients for the maxima and minima in the spectrum of each compound are recorded in Table I, and the complete spectra, measured at 1–5 mμ intervals over the range of 220–600 mμ are represented by the curves in Figures 1, 2, 3 and 4.

In the case of benzalacetophenone (II) exposure to various amounts of light and aging of the solutions in the dark were studied to determine to what extent these factors affect the ultraviolet absorption spectra. See Figure 5.

Discussion of the spectra and structure. This study has resulted in a series of spectra that should be of use in helping to identify the structures of new, related compounds.[2]

In the parent α, β-unsaturated ketone series, Figure 1, the presence of a phenyl group on the β-carbon atom is of more importance than its location on the carbonyl carbon in providing for the longest possible ionic structure with oxygen carrying a charge.



The spectra of ethylideneacetophenone (IV) was found to be quite similar to that of phenylvinyl ketone (λ max., 247.5 mμ, ε, 10,500), as reported by Bowden, *et al.* (16). These structures differ only by a β-methyl group which would not be expected to show a bathochromic effect of more than about 11 mμ (17). Our spectra curves for benzalacetone, benzalacetophenone and their *p*-dimethylamino derivatives were nearly identical with those reported by Alexa (18) using the same type of solvent but a different instrument, see Figures 1 and 4.

The α-amino-α,β-unsaturated ketones, Figure 2, for purposes of discussion, may be divided into four classes, see Table II. All of the known members of this series have been derived from secondary amines. The ionic structures that one can write for any of the α-amino-α,β-unsaturated ketones can be expected to be less stable than those possible for the β-amino ketones which are discussed later.

Although there are no known examples of Class I as yet, we would predict that they would absorb light at shorter wave lengths than their β-amino isomers.

[2] For example see, Cromwell and Eby, (to be published soon), who report that 2-morpholino- and 2-piperidino-4,4-dimethyl-1-keto-1,4-dihydronaphthalene, which are closely related structurally to α-morpholinoethylideneacetophenone (VIII), show maxima at 248–250 mμ, 290–289 mμ, 299–298 mμ and 321–332 mμ.

Class II compounds might be expected to give the general type of absorption shown by compound (VII), since none of the various possible ionic structures would seem to be particularly stable. In Classes III and IV it becomes possible to have ionic structures in which nitrogen may become positive and oxygen negative at the same time. This factor can be expected to enhance the stability of these ionic structures.

Since in Classes III and IV we can also expect the existence of the ionic structures described for Classes I and II it is not surprising that the former show maxima in at least three general areas, (240–250; 270–290; and 330–395 mμ). In Class IV the presence of phenyl groups on both the β-carbon and the carbonyl carbon provides for the longer conjugated unsaturated ionic structure in which

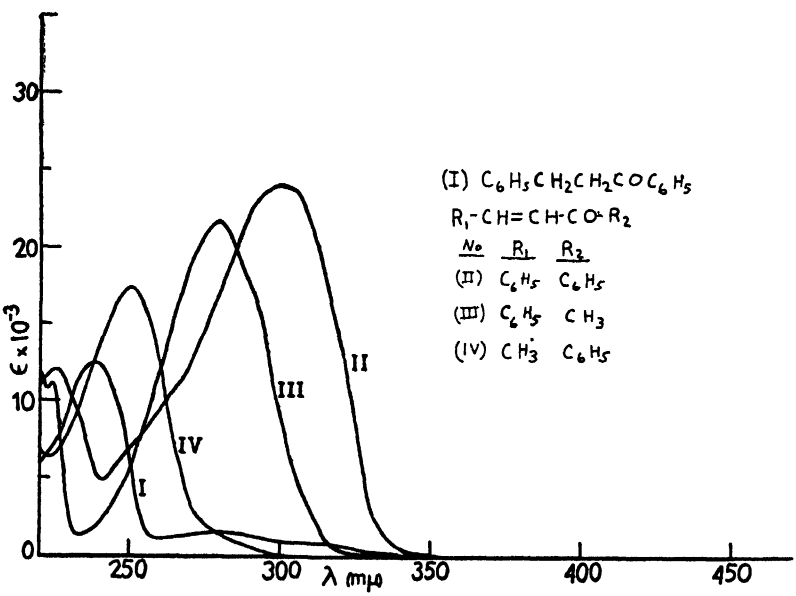


FIG. 1. ABSORPTION SPECTRA OF UNSATURATED KETONES

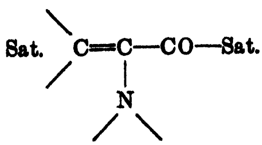
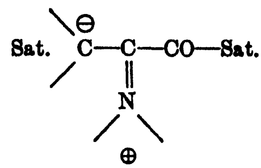
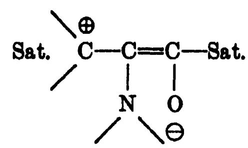
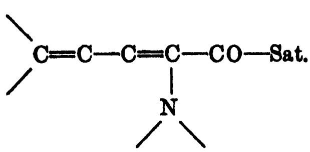
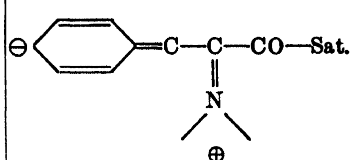
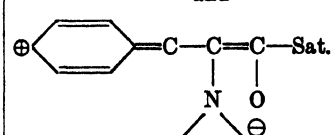
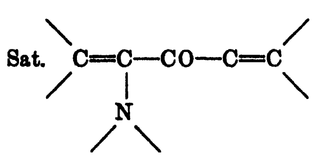
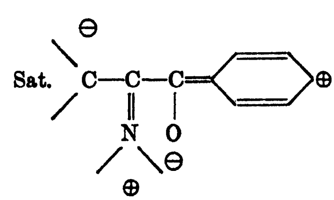
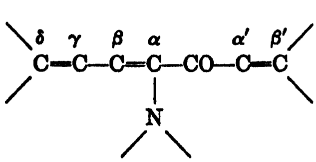
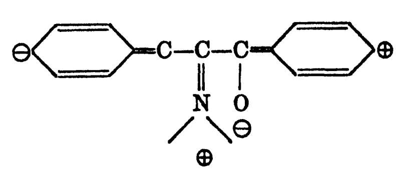
both nitrogen and oxygen carry a charge. Thus these compounds absorb light near the visible range although the intensity is low because the required ionization is inhibited by the energy of the Kekulé resonance of the benzene rings which must be overcome. It is this low, broad-banded maximum at relatively long wave-lengths that is especially typical of the α-amino-α,β-unsaturated ketones, with aryl groups attached to the carbonyl carbon.

The β-amino-α,β-unsaturated ketones, Figure 3, show a short wave-length band between 240 and 250 mμ, and a longer wave-length band above 320 mμ if they are also aryl ketones. Our spectrum for β-morpholinoethylideneacetophenone (XII) is very similar to those reported by Bowden, *et al.* for the β-amino-, β-ethylamino- and β-diethylamino-phenylvinyl ketones (16).

In the β-amino-α,β-unsaturated ketone series the presence of a phenyl group

TABLE II

CLASSES OF α-AMINO-α,β-UNSATURATED KETONES

CLASS		TYPE STRUCTURE (TYPE MAXIMA, mμ)	IMPORTANT IONIC STRUCTURES	EXAMPLES IN TABLE I
No.	Unsaturation			
I	α,β-	 (broad, 250?)	 and 	None known
II	α,β,γ,δ-	 (broad 267)	 and 	(VII)
III	α,β,α′,β′-	 (242; 282; 329)		(VIII)
IV	α,β,α′,β′,γ,δ-	 (248; 286; 392)		(V), (VI)

on the β-carbon has a smaller bathochromic effect on the longer wave-length absorption than in the parent unsaturated ketone series. This may be accounted

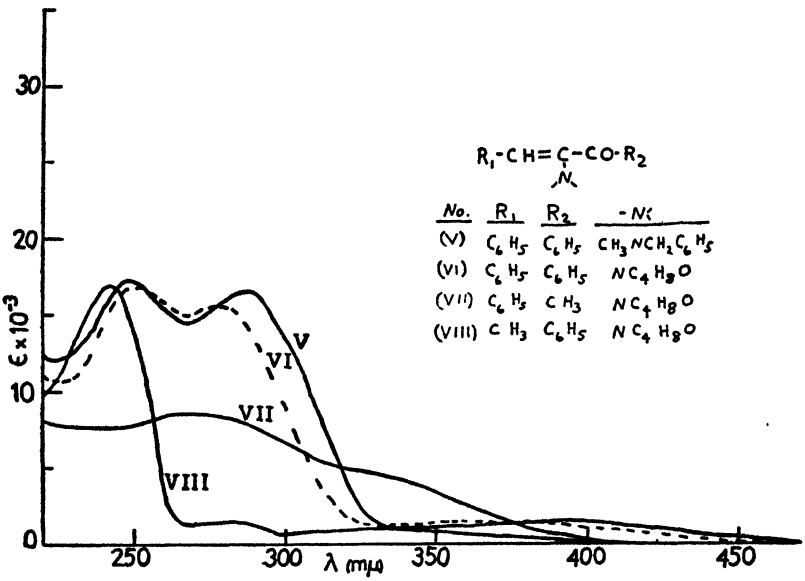


FIG. 2. ABSORPTION SPECTRA OF α-AMINO UNSATURATED KETONES

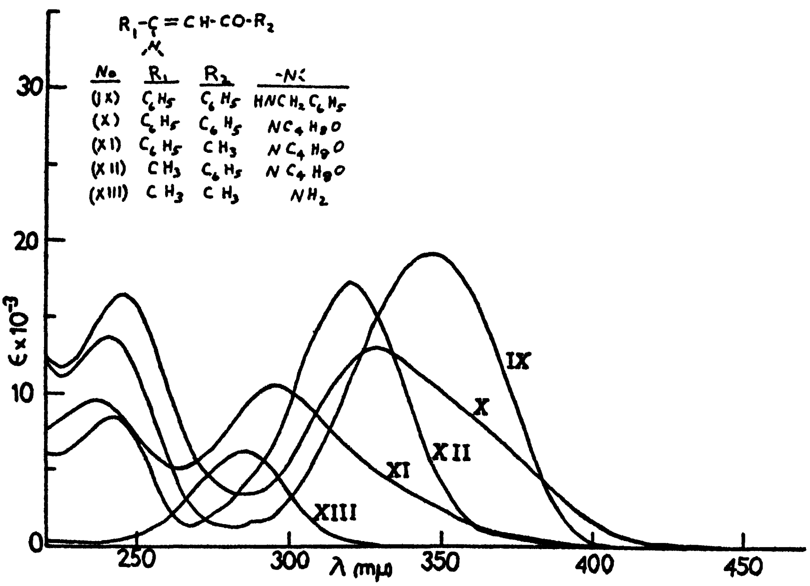
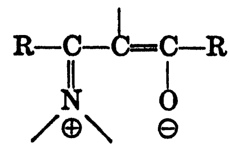


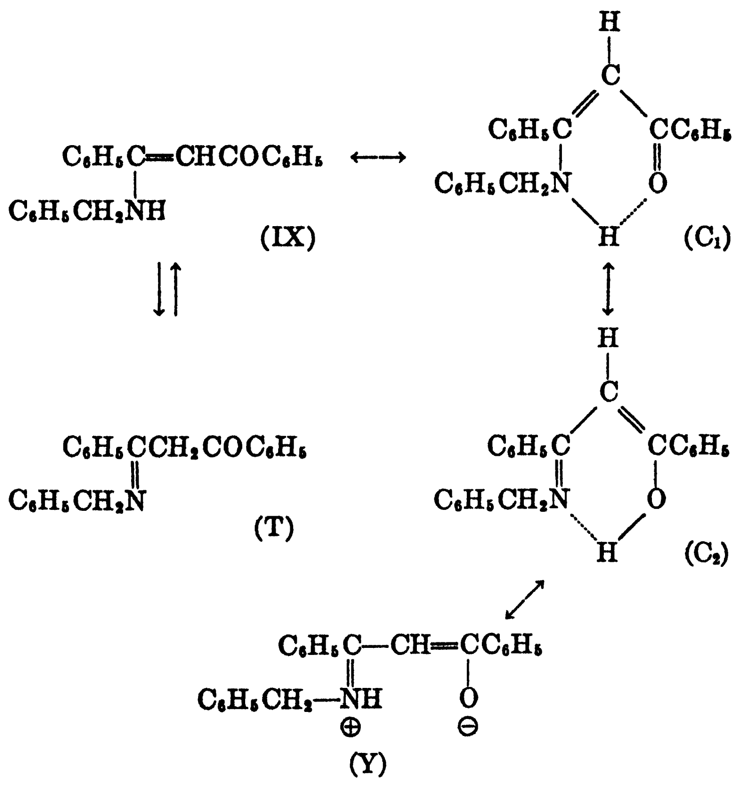
FIG. 3. ABSORPTION SPECTRA OF β-AMINO UNSATURATED KETONES

for by observing that the longer wave-length absorption in this series would seem to be associated with the following ionic form.



The replacement of an alkyl group by a phenyl group on the carbonyl carbon in this series seems to result in a bathochromic effect on the longer wave-length absorption of from 33–46 mμ (see also the results of Bowden, *et al.* (16)). The effects on the longer wave-length spectra of change in the β-amino group will depend on the type of variation. Increased basic strength of the groups should enhance absorption in this region. Introduction of arylamino groups may be expected to provide for interaction between the α,β-unsaturated ketone chromophore and the aromatic ring of the amine (16). The substitution of a simple NH_2 group or a primary amino group, RNH, for a secondary amino radical might be expected to increase the absorption at the longer wave-lengths if other factors, such as basic strength, remained unchanged.

The general shapes of the curves, Figure 3, for (IX) and (X) are the same but the substitution of a primary amino group of greater basic strength for the morpholino group has produced a noticeable bathochromic effect on the longer wave-length absorption. The tautomerism (IX)$\rightleftarrows$(T) would be expected to divide such compounds into two insulated, shorter unsaturated systems. This tauto-



(IX) (C₁) (T) (C₂) (Y)

merism would not be expected to change appreciably the absorption near 240–250 mμ ascribed to the chromophore C_6H_5CO, but would be expected to reduce

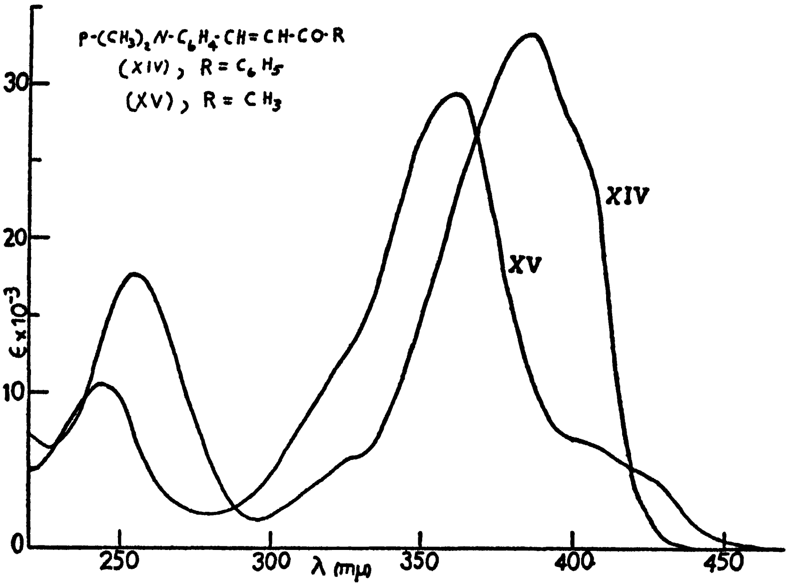


FIG. 4. ABSORPTION SPECTRA OF β-(p-DIMETHYLAMINOPHENYL) UNSATURATED KETONES

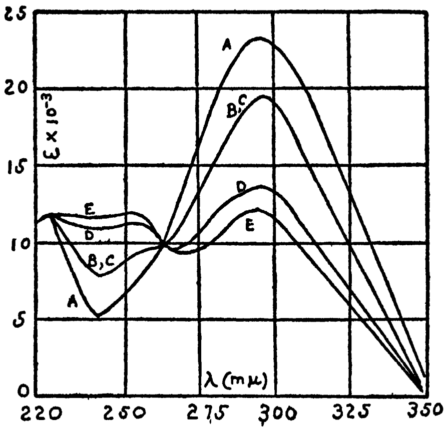


FIG. 5. IRRADIATION EFFECTS ON ULTRAVIOLET ABSORPTION SPECTRUM OF A 0.000025 *M*. SOLUTION OF BENZALACETOPHENONE IN HEPTANE

(A), 80 minutes after preparation, dark storage. (B), after a further 110 minutes in ordinary laboratory daylight, storage in glass volumetric flask. (C), no significant changes after a further dark storage of 30 minutes. (D), after a further 5 minutes of direct sunlight, quartz cell storage. (E), after an additional 20 minutes in direct sunlight, quartz cell storage.

the absorption near 320–325 mμ ascribed to the ionic structure (Y). Conversely, hydrogen-bonding through chelation (IX)↔(C_1)↔(C_2) might be expected to

enhance the stability of the ionic structure (Y). It would seem that there is little or no tendency for the tautomerism, (IX)$\rightleftarrows$(T).

The experiments, Figure 5, on the irradiation of the solutions of benzalacetophenone (chalkone) show that there is a great change in the spectrum after exposure to sunlight. That this is due to the dimerization reported by Stobbe and Bremer (19) seems likely. The decrease in the absorption at 299 mμ, and the increased absorption at shorter wave-lengths (240–250 mμ) may easily be due to the formation of the dimer, which still has the carbonyl groups in conjugation with the benzene nuclei.

It would seem important to protect the dilute solutions of all α,β-unsaturated ketones from direct sunlight before making absorption spectra studies. Such precautions were taken in the present investigation.

SUMMARY

1. The preparation of α-bromo- and α-morpholino-ethylideneacetophenone, and of β-morpholinobenzalacetone have been described.

2. The ultraviolet absorption spectra of fifteen unsaturated ketones or their amino derivatives have been measured in heptane solution over the range of 220–600 mμ.

3. The α-amino-α,β-unsaturated ketones have been classed according to the nature of the ionic resonance or excited structures possible and the characteristic maxima to be expected for each class.

4. Several β-amino-α,β-unsaturated ketones have been studied and the bathochromic effects of phenyl and methyl substituents observed.

5. The possibility of tautomerism and chelation with β-(primary amino)-α,β-unsaturated ketones was discussed from the standpoint of the absorption spectrum of such a compound.

6. The effects of sunlight irradiation on solutions of benzalacetophenone have been studied using ultraviolet absorption spectra measurements and evidence of dimerization as previously shown by Stobbe and Bremer has been obtained.

LINCOLN, NEBRASKA.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF BUFFALO]

STUDIES IN SILICO-ORGANIC COMPOUNDS. VIII. THE PREPARATION AND PROPERTIES OF POLYETHERS FROM TRICHLOROSILANE, CONTINUED[1, 2]

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This work was in effect a continuation of certain investigations already reported (1) which were in turn based on still earlier contributions of others in the field (2, 3, 4, 5).

The action of anhydrous ethyl alcohol on trichlorosilane can be so directed as to form tetraethoxysilane and hydrogen:

$$\text{I} \quad HSiCl_3 + 4C_2H_5OH \rightarrow 3HCl + H_2 + Si(OC_2H_5)_4$$

Hydrogen chloride has a definite part in this reaction as has been demonstrated in the course of this work and its predecessor (1). There was no action when triethoxysilane and ethyl alcohol were refluxed for twenty-four hours but when dry hydrogen chloride was passed through triethoxysilane at 80° a small amount of hydrogen was evolved and some triethoxychlorosilane formed. A mechanism has already been postulated (1).

Hydrogen was also evolved with formation of tetraethoxysilane when dry hydrogen chloride was bubbled through a mixture of refluxing triethoxysilane and ethyl alcohol. Triethoxysilane and moist ethyl alcohol reacted on twenty-four hour reflux to form various hydrolysis products.

To examine the effects of variation in radical size, possible differing effect of dissolved hydrogen chloride, and other factors, on these reactions, trichlorosilane was allowed to react separately with several different alcohols including phenol both with and without benzene as a solvent. Yields of trialkoxy- and tetra-alkoxy-silanes are reported in Table I.

In addition, the data already presented (1) with respect to ethyl, *n*-propyl, and *n*-butyl analogs were checked. *t*-Butyl alcohol led only to what was probably a polymerized 1,3-dioxodisiloxane, a hydrolysis product:

$$\text{II} \quad t\text{-}C_4H_9OH + HCl \rightarrow HOH + t\text{-}C_4H_9Cl$$
$$\text{III} \quad 2xHSiCl_3 + 3xHOH \rightarrow 6xHCl + (HSiO_{1.5})x$$

Hydrolysis products also resulted from the interaction of allyl alcohol and trichlorosilane. Trialloxysilane polymerized at the boiling point, 188° (760 mm). There was almost no evolution of hydrogen from the reaction using benzyl alcohol. After excess benzyl alcohol had been distilled from the reaction mixture, contact with sodium hydroxide showed the residue to be largely tribenzoxysilane. However, only tetrabenzoxysilane could be isolated on distillation. It has

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already been reported by Friedel and Ladenburg (2) that trialkoxysilanes will disproportionate at high temperatures.

With carefully regulated amounts of water, triethoxysilane was hydrolyzed to 1,1,3,3,-tetraethoxydisiloxane along with considerable amounts of gel-like substances. The presence of ether reduced the yield of the latter to a trace.

TABLE I

YIELDS OF POLYETHERS (IN PER CENT)

	ATTEMPTED SYNTHESIS OF			
	$HSi(OR)_3$		$Si(OR)_4$	
	With C_6H_6	Without C_6H_6	With C_6H_6	Without C_6H_6
$HSi(OC_4H_9\text{-}s)_3$	56.6	53.5	0	0
$HSi(OC_5H_{11}\text{-}n)_3$	42.5	26.4	6.5	19
$HSi(OC_6H_{13}\text{-}n)_3$	48.3	43	9.8	?
$HSi(OC_7H_{15}\text{-}n)_3$	47	45	6.7	6.3
$HSi(OCH_2CH{=}CH_2)_3$	42.2	28	?	13
$HSi(OCH_2C_6H_5)_3$	0	0	100	100
$HSi(OC_6H_5)_3$	100	100	0	0

TABLE II

PHYSICAL PROPERTIES OF POLYETHERS

COMPOUND	B.P. °C/MM.	n_D^t	d_4^t
$HSi(OC_4H_9\text{-}s)_3$	213–215/760	1.4054^{20}	0.8661^{20}
$HSi(OC_5H_{11}\text{-}n)_3$	132–135/5	1.4210^{20}	0.8710^{27}
		1.4195^{27}	
$HSi(OC_6H_{13}\text{-}n)_3$	164–170/5	1.4284^{20}	0.8701^{25}
	180–185/10	1.4270^{25}	
	195–198/15		
$HSi(OC_7H_{15}\text{-}n)_3$	194–196/5	1.4330^{20}	0.8713^{26}
	197–203/7	1.4315^{26}	
	208–210/10		
$HSi(OCH_2CH{=}CH_2)_3$	110–112/14	1.4284^{20}	0.9836^{25}
	114–116/28	1.4270^{25}	
	188–190/760		
$HSi(OC_6H_5)_3$	175–177/3	1.5636^{20}	1.1158^{26}
	193–195/8	1.5621^{26}	
	206–208/12		
$[(C_2H_5O)_2SiH]_2O$	94–97/25	1.3850^{25}	

As a further check on the structure and identity of each compound, molecular refractions were calculated in two ways, first by means of the conventional $N = \dfrac{M}{d}\dfrac{n^2 - 1}{n^2 + 2}$ and again by means of bond refractive values as presented by Warrick (7).

Alkoxychlorosilanes were prepared by allowing the selected alcohol to react with trichlorosilane in benzene in carefully regulated molar ratio. Mixed

polyalkoxysilanes were prepared by treating the proper chloro compound made as indicated above, with the desired alcohol, also in benzene. Disproportionation was a strong factor here.

TABLE III

COMPARATIVE VALUES; MOLECULAR REFRACTIONS

POLYETHER	A	B
$HSi(OC_4H_9\text{-}s)_3$	70.41	69.45
$HSi(OC_5H_{11}\text{-}n)_3$	84.16	83.84
$HSi(OC_6H_{13}\text{-}n)_3$	97.95	97.68
$HSi(OC_7H_{15}\text{-}n)_3$	111.25	111.62
$HSi(OCH_2CH{=}CH_2)_3$	52.21	52.03
$HSi(OC_6H_5)_3$	89.68	87.14
$[(C_2H_5)_2SiH]_2O$	62.40	62.60
$HSi(OC_4H_9\text{-}n)_2OC_5H_{11}\text{-}n$	75.15	74.60
$HSi(OC_5H_{11}\text{-}n)_2OC_4H_9\text{-}n$	79.54	79.32
$(n\text{-}C_4H_9O)_3SiOC_2H_5$	79.60	79.24
$(n\text{-}C_4H_9O)_3SiNHC_6H_5$	98.26	96.28
$(n\text{-}C_4H_9O)_3SiN(C_2H_5)_2$	91.36	91.62
$HSi(OC_4H_9\text{-}n)_2NHC_6H_5$	77.28	76.83

$A = \frac{M}{d}\frac{n^2 - 1}{n^2 + 2}$ B = bond refractions

TABLE IV

PHYSICAL PROPERTIES; MIXED COMPOUNDS

COMPOUND	B.P. °C/MM.	n_D^t	d_4^t
$ClSiH(OC_4H_9\text{-}n)_2$	88–92/17 180–182/760		0.9450^{27}
$Cl_2SiHOC_4H_9\text{-}n$	126–128/760		
$(C_2H_5O)_2SiHOC_4H_9\text{-}n$[a]	155–165/760		0.8866^{25}
$C_2H_5OSiH(OC_4H_9\text{-}n)_2$[a]	190–198/760		
$(n\text{-}C_5H_{11}O)_2SiHOC_4H_9\text{-}n$[a]	117–119/2	1.4184^{20} 1.4170^{24}	0.8759^{24}
$n\text{-}C_5H_{11}OSiH(OC_4H_9\text{-}n)_2$[a, b]	132–134/18	1.459^{18}	0.8742^{18}
$(n\text{-}C_4H_9O)_3SiNHC_6H_5$	204–208/25	1.4664^{20}	0.9598^{20}
$(n\text{-}C_4H_9O)_3SiHN(C_2H_5)_2$	159–160/25	1.4208^{24}	0.8846^{24}
$HSi(OC_4H_9\text{-}n)_2NHC_6H_5$[b]	169–173/25	1.4550^{24}	0.9550^{24}
$(n\text{-}C_4H_9O)_3SiOC_2H_5$[c]	144–146/20	1.4112^{20}	0.9442^{25} 0.9010^{20}

[a] From $Cl_2SiHOC_4H_9\text{-}n$.
[b] From $ClSiH(OC_4H_9\text{-}n)_2$.
[c] Previously reported by Peppard, Brown, and Johnson (12); b.p. 150–150.5°/32 mm.; n_D^{30} 1.4075.

The tendency toward disproportionation decreased with rise of molecular weight as in the field of the carbon orthoesters.

Tributoxyanilinosilane and tributoxydiethylsilazine were prepared from tributoxychlorosilane:

IV $2C_6H_5NH_2 + ClSi(OC_4H_9\text{-}n)_3 \rightarrow (n\text{-}C_4H_9O)_3SiNHC_6H_5 + C_6H_5NH_3Cl$

V $2(C_2H_5)_2NH + ClSi(OC_4H_9\text{-}n)_3 \rightarrow (n\text{-}C_4H_9O)_3SiN(C_2H_5)_2 + (C_2H_5)_2NH_2Cl$

A similar reaction took place with dibutoxychlorosilane:

VI $2C_6H_5NH_2 + ClSiH(OC_4H_9\text{-}n)_2 \rightarrow (n\text{-}C_4H_9O)_2SiHNHC_6H_5 + C_6H_5NH_3Cl$

EXPERIMENTAL

Tri-n-Amoxysilane was prepared by the interaction of 50 cc. of anhydrous *n*-amyl alcohol (0.5 mole) and 15 cc. (0.15 mole) of trichlorosilane, all at 0° using 50 cc. of benzene as solvent. Tri-*n*-amoxysilane, b.p. 132–135° (5 mm.), d_4^{27} 0.8710, n_D^{20} 1.4210, n_D^{27} 1.4195. *Si* (found) 9.70, 9.72; (calc'd) 9.66. *Mol. wt.* (cryoscopic in benzene) (found) 288, 293; (calc'd) 291.45. *Hydrogen* (by caustic treatment) (found) 158 cc.; (calc'd) 157 cc. Yield 42.5% with benzene, 26.4% without. Tetra-*n*-amoxysilane was isolated as a by-product from the reaction. Yield, in benzene, 6.5%; without benzene, 19%.

Tri-n-Hexoxysilane was prepared in a manner analogous to that used for tri-*n*-amoxysilane, b.p. 164–170° (5 mm.); 180–185° (10 mm.); 195–198° (15 mm.). d_4^{28} 0.8701; n_D^{20} 1.4284; n_D^{28} 1.4270. *Hydrogen* (found) 71 cc.; (calc'd) 70 cc. *Si* (found) 9.40, 9.35; (calc'd) 9.25. Yield 48.3% with benzene, 43% without. Yield of *tetra-n-hexoxysilane:* with benzene 9.8%, without, small amount. B.p. 187–188° (5 mm.); 232–234° (20 mm.).

Tri-n-Heptoxysilane was also prepared in the manner outlined above. B.p. 194–196° (5 mm.); 197–203° (7 mm.); 208–210° (10 mm.); d_4^{28} 0.8713; n_D^{20} 1.4330; n_D^{28} 1.4315. *Hydrogen* (found) 200 cc., (calc'd) 203 cc. *Si* (found) 7.58, 7.52; (calc'd) 7.48. *Mol. wt.* (found) 370; (calc'd) 374. Yield 47% in benzene, 45% without benzene. *Tetra-n-heptoxysilane*, b.p. (found 212–215° (5 mm.); literature (8) 200–215° (3 mm.), was found in 6.7% yield with benzene and 6.3% without.

Tri-s-Butoxysilane was prepared as the above polyethers, using 0.75 mole of alcohol and 0.25 mole of trichlorosilane with 50 cc. of benzene, giving tri-s-butoxysilane, b.p. 213–215° (755 mm.); d_4^{20} 0.8661; n_D^{20} 1.4054. *Hydrogen* (found) 118 cc., (calc'd) 121 cc.; *Si* (found) 11.15, 11.22; (calc'd) 11.30. *Mol. wt.* (found) 252, 249; (calc'd) 248. Yield 56.6% with benzene, 53.5% without. There was a small yield in each case of higher boiling, perhaps hydrolyzed, products but no isolable tetra-s-butoxysilane.

Trialloxysilane was prepared in the above manner with anhydrous allyl alcohol and trichlorosilane in the molar ratio of 0.8/0.25 respectively in 50 cc. of benzene. Trialloxysilane, b.p. 110–112° (14 mm.); 114–116° (28 mm.); 188–190° (760 mm.); d_4^{28} 0.9836; n_D^{20} 1.4284. *Hydrogen* (found) 96 cc., (calc'd) 94.4 cc.; *Si* (found) 13.60, 13.86; (calc'd) 14.0. *Mol. wt.*, (found) 205, 202; (calc'd) 200. Yield 42.2% with benzene, 28% without benzene. Higher boiling products were also obtained but could not be identified, save for small amount formed without benzene, probably *tetraalloxysilane*, in 13% yield. B.p. 114–116° (12 mm.); 135–136° (25 mm.); literature (5) 115–116° (13 mm.).

Benzyl alcohol and trichlorosilane. When anhydrous benzyl alcohol (0.8 mole) and trichlorosilane (0.25 mole) reacted at 0° in 50 cc. of benzene only tetrabenzoxysilane resulted. Before distillation, caustic treatment showed a content of about 91% of theoretical silane hydrogen but on distillation only *tetrabenzoxysilane* came over, b.p. 260–262° (1 mm.); m.p. 32.0–32.5°, literature (5) 32.0°; 46.5% yield. No significant change could be noted in the nature of the products when benzene was omitted.

Triphenoxysilane was prepared by treating 50 g. of anhydrous phenol (0.54 mole) with 15 cc. (0.15 mole) of trichlorosilane and 50 cc. of benzene, at 0°. The experimental details were the same as in the preceding experiments. After distilling off excess phenol there was obtained a 68.2% yield of triphenoxysilane, b.p. 175–177° (3 mm.); 193–195° (8 mm.); 206–

208° (12 mm.); d_4^{20} 1.1158; n_D^{20} 1.5636. *Hydrogen* (found) 94 cc., (calc'd) 96 cc.; *Si* (found) 9.13, 9.15; (calc'd) 9.09. *Mol. wt.* (found) 313, 315; (calc'd) 308. The yield without benzene was 65.5%. In no case was any other product detectable.

Tri-n-Butoxysilane, Aniline, and Lithium. Tri-*n*-butoxysilane, 37 g., (0.145 mole) was added dropwise to 18 g. (0.193 mole) of aniline and 50 cc. of benzene. Lithium, 1 g. (0.145 atom) was added as a catalyst. The mixture was stirred at room temperature for 12 hours and then refluxed for 1 hour. A gas was evolved during the course of the reaction and the system became darker in color. After excess aniline and benzene had been removed, 21.6 g. of *tetra-n-butoxysilane* was isolated, b.p. 160–162° (22 mm.), literature 160° (20 mm.) (8); n_D^{20} 1.4124, literature 1.4128 (8); yield 40%. Considerable polymerized material, soluble in benzene and in ether, was also obtained.

Tri-n-Butoxysilane and Alcoholic Potassium Hydroxide. Tri-*n*-butoxysilane, 25 g., (0.10 mole) was dissolved in an excess of anhydrous ethyl alcohol. A saturated solution of potassium hydroxide in ethyl alcohol was added dropwise with mechanical stirring at room temperature until evolution of hydrogen was observed. After the evolution of hydrogen had stopped, dry carbon dioxide was passed into the solution to precipitate the potassium hydroxide as potassium carbonate. The mixture was filtered, dried over sodium sulfate and fractionated, giving 22.5 g. of *ethoxytri-n-butoxysilane*, b.p. 144–145° (20 mm.); d_4^{20} 0.9010; n_D^{20} 1.4112; yield 77%. *Si* (found) 9.61, 9.54; (calc'd) 9.58. A clear colorless liquid, hydrolyzing in water and caustic, more readily in acids. Ethoxytri-*n*-butoxysilane was also prepared by the interaction of tri-*n*-butoxychlorosilane and absolute ethyl alcohol in the presence of pyridine, b.p. 150–152° (25 mm.); n_D^{20} 1.4110, *Mol. wt.* (found) 287, 284; (calc'd) 292; yield 58%.

Hydrolysis of triethoxysilane. Triethoxysilane, 100 g. (0.625 mole), was dissolved in 100 cc. of absolute ethyl alcohol and 5 cc. (0.28 mole) of water was added. The mixture was refluxed for 24 hours and fractionated, giving 20 g. of *1,1,3,3-tetraethoxydisiloxane*, b.p. 88–92° (22 mm.); 94–97° (25 mm.); d_4^{25} 0.9442; n_D^{20} 1.3864. *Hydrogen* (found) 77 cc.; (calc'd) 79 cc.; *Si* (found) 22.1, 22.1; (calc'd) 22.06; *Mol. wt.* (found) 258, 250; (calc'd) 254; yield 28%, a colorless, oily liquid hydrolyzing slowly in water, rapidly in caustic.

A mixture of 100 g. of triethoxysilane in ether and 5 cc. of water was refluxed for 36 hours, forming 1,1,3,3-tetraethoxydisiloxane in 25.5% yield. Triethoxysilane, 30 g., was also hydrolyzed by stirring with excess *N* hydrochloric acid on a water bath for 8 hours; there was a slow formation of a white flocculent precipitate, probably polymerized *1,3-dioxodisiloxane*. *Hydrogen* (found) 366 cc.; (calc'd) 369 cc.; *Si* (found) 52.7, 52.7; (calc'd) 52.73. Insoluble in water, acids or organic solvents, but soluble in caustic with evolution of hydrogen.

Triethoxysilane, 50 g., (0.34 mole) was dissolved in 200 cc. of anhydrous ether and 2.5 cc. of *N* sodium hydroxide in 600 cc. of ether was added slowly, with stirring for 24 hours, at room temperature. Hydrogen was slowly evolved and a white precipitate appeared. The ether solution was washed with cold water to remove caustic, then dried over calcium chloride. From this material there was obtained 14.3 g. of *hexaethoxydisiloxane*, b.p. 230–232° (760 mm.), in agreement with the literature (9); yield 31%.

n-Butoxydichlorosilane was prepared by the interaction of 27 cc. (0.30 mole) of anhydrous *n*-butyl alcohol and 0.30 mole of trichlorosilane, in 50 cc. of benzene, at 0° to 30°. The mixture was stirred at room temperature for three hours. It was then refluxed gently to remove dissolved hydrogen chloride. *n*-Butoxydichlorosilane was isolated in 30% yield, b.p. 126–128° (760 mm.) (*Cl.* found 41.0, 40.2; calc'd, 40.5), and di-*n*-butoxychlorosilane in 11.8% yield, b.p. 179–182° (760 mm.). There was a small amount of higher boiling products.

Di-n-Butoxychlorosilane was prepared as was the above compound save that 0.4 mole of alcohol was used with 0.2 mole of trichlorosilane. There were isolated *n*-butoxydichlorosilane, b.p. 126–129° (760 mm.); di-*n*-butoxychlorosilane, b.p. 88–92° (17 mm.); 180–182° (760 mm.); d_4^{27} 0.9450. [*Cl* (found) 16.80, 16.92; (calc'd) 16.86; *Mol. wt.* (found) 213, 218; (calc'd) 210.5], and tributoxysilane, b.p. 120–122° (17 mm.). The yield of di-*n*-butoxychlorosilane was 40.3%, of *n*-butoxydichlorosilane 6%, and of tri-*n*-butoxysilane, 12%.

Di-*n*-butoxychlorosilane is a colorless liquid fuming slightly in air. It hydrolyses rapidly in water, caustic and acid.

n-Amoxydi-n-Butoxysilane was prepared by the action of 8 cc. (0.76 mole) of anhydrous amyl alcohol on 14 g. (0.068 mole) of di-*n*-butoxychlorosilane. The mixture was stirred at room temperature for three hours, then refluxed for one hour. Fractionation was carried out with an all-glass, glass-helix packed fractionating-column. *n*-Amoxydi-*n*-butoxysilane was isolated in 45% yield, b.p. 132–134° (18 mm.); d_4^{18} 0.8742; n_D^{20} 1.4156. *Hydrogen* (by caustic treatment) (found) 63.5 cc.; (calc'd) 65.5 cc.; *Si* (found) 10.72, 10.78; (calc'd) 10.69. A colorless, oily liquid, hydrolyzing in water, faster in caustic or acid. A small amount of tri-*n*-butoxysilane was also isolated, b.p. 120–122° (18 mm.).

n-Butoxydi-n-Amoxysilane was prepared in the same manner, save that 0.27 mole of anhydrous *n*-amyl alcohol was used with 0.133 mole of *n*-butoxydichlorosilane. *n*-Butoxy-di-*n*-amoxysilane was isolated in 55% yield; b.p. 117–119° (2 mm.); d_4^{25} 0.8759; n_D^{20} 1.4164. *Hydrogen* (by caustic treatment) (found) 27.2 cc.; (calc'd) 26.8 cc.; *Si* (found) 10.1, 10.1; (calc'd) 10.15; C (found) 60.50; (calc'd) 60.40. H (found) 11.89; (calc'd) 11.67. *Mol. wt.* (found) 270, 279; (calc'd) 276. *Tri-n-amoxysilane* was also isolated, b.p. 127–129° (2 mm.), in 12% yield; n_D^{20} 1.4215, d_4^{20} 1.4212.

n-Butoxydichlorosilane and Ethyl Alcohol. Anhydrous ethyl alcohol, 13 g. (0.28 mole), was added dropwise with stirring at 0° to a solution of 24 g. (0.14 mole) of *n*-butoxydichlorosilane and 50 cc. of benzene. The same experimental conditions were observed as in the preceding experiments on the preparation of mixed alkoxysilanes. Distillation at 760 mm. gave 7 g. of *triethoxysilane*, b.p. 133–135°, 5.7 g. of *n-butoxydiethoxysilane*, b.p. 155–165°, and 5.0 g. of *di-n-butoxyethoxysilane*, b.p. 190–198°. The remainder distilled between 210° and 240°; then decomposed. The results cannot be regarded as conclusive owing to the wide boiling range of these products. Fractionation was carried out with a glass-helix packed-column. *n-Butoxydiethoxysilane* (impure), b.p. 155–165° (760 mm.); d_4^{25} 0.8866. *Hydrogen* (by caustic treatment) (found) 458 cc.; (calc'd) 459 cc. *Si* (found) 14.56; (calc'd) 14.58.

Tri-n-butoxyanilinosilane was prepared by adding dropwise 121 cc. (1.32 moles) of an hydrous butyl alcohol to 50 cc. (0.44 mole) of tetrachlorosilane. After stirring for 24 hours, the mixture was fractionated. *Tri-n-butoxychlorosilane* was formed in 64.5% yield; b.p. 125–128° (10 mm.), literature 126–128° (10 mm.) (10). Tri-*n*-butoxychlorosilane, 25 g. (0.088 mole), was added dropwise to 18 g. (0.19 mole) of aniline and 50 cc. of benzene. After stirring for 24 hours at room temperature the mixture was filtered and the remaining liquid washed with cold water. After drying over calcium chloride and removing excess benzene and aniline, the pressure was lowered and other unreacted material distilled off followed by 17.0 g. of *tri-n-butoxyanilinosilane*, b.p. 198–201° (20 mm.); 204–208° (25 mm.). A colorless oily liquid, d_4^{20} 0.9598; n_D^{20} 1.4684. *Si* (found) 8.28, 8.30; (calc'd) 8.26. *Mol. wt.* (found) 341, 339; (calc'd) 339; yield 56.7%. Tri-*n*-butoxyanilinosilane hydrolyzes slowly in water and caustic, faster in acid, the latter forming aniline hydrochloride, silica and butyl alcohol.

Tri-n-Butoxysilyldiethylamine was prepared by adding 20 g. (0.071 mole) of tri-*n*-butoxy-chlorosilane dropwise to 16 cc. (0.15 mole) of diethylamine and 50 cc. of benzene. After stirring for 24 hours at room temperatures the mixture was refluxed for 2 hours to coagulate the amine hydrochloride. Diethylammonium chloride was filtered and the liquid washed with cold water. After drying over calcium chloride and removing excess benzene and diethylamine there was isolated 15 g. of *tri-n-butoxysilyldiethylamine*, b.p. 145–147° (13 mm.); 149–150° (14 mm.); 159–160° (25 mm.). *Si* (found) 8.81, 8.83; (calc'd) 8.79. *Mol. wt.* (found) 324, 325; (calc'd) 319; yield 45.5%. Tri-*n*-butoxysilyldiethylamine is a colorless, oily liquid, hydrolyzing slowly in water or caustic but more rapidly in acids.

Di-n-Butoxyanilinosilane was formed by the interaction of 30 g. (0.14 mole) of di-*n*-butoxychlorosilane and 28 cc. (0.29 mole) of aniline in 50 cc. of benzene. The liquid products were distilled without washing. Di-*n*-butoxyanilinosilane, 15 g., 39.2% yield; b.p. 169–173° (25 mm.); 183–184° (30 mm.); d_4^{20} 0.9550; n_D^{25} 1.4646. *Hydrogen* (found) 56.9 cc.; (calc'd) 58 cc. *Si* (found) 10.53, 10.58; (calc'd) 10.48. *Mol. wt.* (found) 263; (calc'd) 267. An oily, colorless liquid hydrolyzing slowly in water, more rapidly in caustic and acids.

Hydrogen was determined by placing a weighed sample of the material in a flask with a side-arm delivery tube. Sodium hydroxide, 30%, was added through a dropping-funnel and the hydrogen collected by water displacement.

Silicon was determined on approximately half-gram samples by treatment first with 7 or 8 cc. of 40% perchloric acid. After standing for fifteen minutes to insure complete precipitation, the system was diluted to 200 cc. and filtered. The precipitate was washed with 1% hydrochloric acid, then ignited in a platinum crucible to constant weight. The silicon dioxide was destroyed by treatment with 1 cc. of hydrofluoric acid. The crucible was then heated as before to constant weight.

Chlorine was determined according to the method given by Rochow (11).

Trichlorosilane, alcohols, etc., were obtained from manufacturing sources and showed satisfactory physical properties.

SUMMARY

1. It has been shown that certain aliphatic alcohols will react with trichlorosilane to form the corresponding tetraalkoxysilanes with evolution of hydrogen. With benzene as a solvent this reaction runs its normal course however to form the trialkoxysilane. These reactions have been carried out beyond the work previously recorded (1) using *s*-butyl, *n*-amyl, *n*-hexyl, *n*-heptyl, allyl and benzyl alcohols as well as phenol.

2. The action of aqueous and alcoholic potassium hydroxide has been further studied and the identities of many of the products determined. Acid, basic, and neutral hydrolytic reactions have been run on the above trialkoxysilanes. 1,1,3,3-Tetraethoxydisiloxane has been prepared in this manner.

3. Tribenzoxysilane disproportionates when heated giving tetrabenzoxysilane.

4. Molecular refractions of the various products were determined through the use of the Lorenz-Lorentz formula and by means of bond refraction values presented by Warrick (7).

5. Di-*n*-butoxychlorosilane and *n*-butoxydichlorosilane have been prepared by the interaction of trichlorosilane and regulated amounts of anhydrous *n*-butyl alcohol. The interaction of anhydrous ethyl alcohol and *n*-butoxydichlorosilane formed *n*-butoxydiethoxysilane and di-*n*-butoxyethoxysilane. Anhydrous *n*-amyl alcohol reacted similarly. *n*-Amoxydi-*n*-butoxysilane was also prepared by the action of anhydrous *n*-amyl alcohol on di-*n*-butoxychlorosilane. The action of anhydrous ethyl alcohol on *n*-butoxydichlorosilane also gave rise to disproportionation.

6. Tri-*n*-butoxychlorosilane was prepared by the action of anhydrous *n*-butyl alcohol on tetrachlorosilane. When this product reacted with dry aniline in benzene, tri-*n*-butoxyanilinosilane was formed. In similar manner, di-*n*-butoxyanilinosilane was also preapred. Tri-*n*-butoxychlorosilane and diethyl amine reacted to form tri-*n*-butoxysilyldiethylamine.

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[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

ALKYLATION REACTIONS OF TETRAETHYLLEAD. A NEW SYNTHESIS OF ETHYLDICHLOROARSINE AND RELATED COMPOUNDS[1]

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The methods described in the literature for the preparation of ethyldichloroarsine and the analogous compounds of phosphorus and antimony are rather involved. For example, the preparation of ethyldichloroarsine (1) involves the following three steps.

1. Treatment of sodium arsenite with ethyl chloride or ethyl sulfate to form disodium ethylarsonate.

$$Na_3AsO_3 + C_2H_5Cl \rightarrow C_2H_5AsO_3Na_2 + NaCl$$
$$Na_3AsO_3 + (C_2H_5O)_2SO_2 \rightarrow C_2H_5AsO_3Na_2 + NaOSO_2OC_2H_5$$

2. The reduction of disodium ethylarsonate with sulfur dioxide to form ethylarsenious oxide.

$$C_2H_5AsO_3Na_2 + SO_2 \rightarrow C_2H_5AsO + Na_2SO_4$$

3. The treatment of ethylarsenious oxide with hydrogen chloride to form ethyldichloroarsine.

$$C_2H_5AsO + 2HCl \rightarrow C_2H_5AsCl_2 + H_2O$$

The method developed in this laboratory for the preparation of ethyldichloroarsine and the analogous compounds of phosphorus and antimony consists in treating arsenic trichloride with tetraethyllead. The over-all reaction is

$$Pb(C_2H_5)_4 + 3AsCl_3 \rightarrow 3C_2H_5AsCl_2 + C_2H_5Cl + PbCl_2$$

The reaction appears to proceed in two stages. The first stage

$$Pb(C_2H_5)_4 + 2AsCl_3 \rightarrow (C_2H_5)_2PbCl_2 + 2C_2H_5AsCl_2$$

proceeds spontaneously at room temperature. At temperatures below 50°, however, even an excess of arsenic trichloride will not detach a third ethyl radical from the diethyllead dichloride. The second stage

$$(C_2H_5)_2PbCl_2 + AsCl_3 \rightarrow C_2H_5AsCl_2 + PbCl_2 + C_2H_5Cl$$

proceeds slowly at 80° and rapidly at temperatures above 90°.

The reaction may be carried out either in the presence or absence of solvents. When low-boiling solvents are used only the first stage occurs. When the reaction is carried out at temperatures above 80°, either without a solvent or with

[1] This paper is based in whole on work done for the Office of Scientific Research and Development under Contract No. OEMsr-394 with the University of Chicago.

a high-boiling solvent (*e.g.*, nitrobenzene) both stages proceed simultaneously. The ethyl chloride is readily recovered by chilling the evolved gases.

The synthesis was found to be most convenient when no solvent was used; tetraethyllead was slowly dropped into the calculated amount of arsenic trichloride with stirring at 100°. The product was then distilled directly from the solid lead chloride produced. Under these conditions, the yield of ethyldichloroarsine was from 95 to 97% of the calculated amount.

At higher temperatures (120°) ethyldichloroarsine reacts further with excess tetraethyllead to form diethylchloroarsine

$$2C_2H_5AsCl_2 + Pb(C_2H_5)_4 \rightarrow 2(C_2H_5)_2AsCl + (C_2H_5)_2PbCl_2$$

Diethylchloroarsine is much less stable than ethyldichloroarsine; on contact with air it instantly begins to form a white solid.

Ethylarsenious oxide was prepared from ethyldichloroarsine. The high-boiling point of ethylarsenious oxide (158°/10 mm.) as compared with that of ethyldichloroarsine (74°/50 mm.) led us to examine the molecular weight of the oxide. The molecular weight (in benzene) of ethylarsenious oxide is 376. The compound is, therefore, a trimer $(C_2H_5AsO)_3$, and not a monomolecular compound as it is represented by all investigators and in all texts on the chemistry of organic arsenicals.

When phosphorus trichloride and antimony trichloride were treated with tetraethyllead in a manner similar to that described for arsenic trichloride, wholly analogous reactions occurred.

$$Pb(C_2H_5)_4 + 3PCl_3 \rightarrow 3C_2H_5PCl_2 + PbCl_2 + C_2H_5Cl$$
$$Pb(C_2H_5)_4 + 3SbCl_3 \rightarrow 3C_2H_5SbCl_2 + PbCl_2 + C_2H_5Cl$$

The yields of ethyldichlorophosphine obtained were excellent, varying from 89 to 96%. In the only reaction carried out with antimony trichloride the yield of ethyldichlorostibine was 71%.

EXPERIMENTAL

Materials used. The tetraethyllead used in these experiments was the commercial product obtained from the Ethyl Gas Corporation. Two types of arsenic trichloride were used, a technical-grade material obtained from the Hooker Chemical Company and a reagent-grade material obtained from the J. T. Baker Chemical Company. The yields and product purity were identical with both grades of arsenic trichloride.

The phosphorus trichloride was reagent-grade material obtained from the General Chemical Company.

The antimony trichloride was a C.P. grade obtained from Eimer and Amend.

Preparation of ethyldichloroarsine. The reaction should be carried out in an efficient hood, preferably one equipped with windows which can be closed. In handling either the reactants or the products, rubber gloves and a gas mask should be worn.

A five-liter three-necked flask was fitted with a 250-ml. dropping-funnel, an efficient mechanical stirrer, and a one-meter bulb condenser leading to a 500-ml. trap cooled with Dry Ice and acetone. In the flask was placed 2730 g. (15 moles) of arsenic trichloride; the air in the flask was then swept out with a current of nitrogen. The flask was heated to 100° and, after the arsenic trichloride had reached that temperature, a few cubic centimeters of

tetraethyllead was added from the dropping-funnel to the stirred arsenic trichloride. The start of the reaction (which occurred in a few minutes) was indicated by clouding of the liquid and separation of a white precipitate. A total of 1620 g. (5 moles) of tetraethyllead was then added through the dropping-funnel at such a rate that the reaction mixture kept gently boiling. During this addition of the tetraethyllead, and for one hour after the addition, the mixture was vigorously agitated. The oil-bath temperature was maintained at 100–110°. About seven hours was required for the addition of tetraethyllead.

After the product had cooled to room temperature (usually by standing overnight), the condenser, dropping-funnel and stirrer were removed, the side necks were closed with ground-glass stoppers, and the center neck was fitted with a Claisen still-head. The product was distilled directly from the reaction mixture at 75 mm. During the distillation, the oil-bath was maintained at 120°; the product distilled at 82–83°. About 80% of the product distilled in four to five hours. The distillation of the remainder was very slow, because of the large amount of lead chloride in the flask. The distillation process may be hastened by gradually reducing the pressure further. It required about 10 hours to distill 2500 g. of ethyldichloroarsine. The yield in this experiment was 95% of the calculated amount. In other experiments yields as high as 97% were obtained.

The density of the crude, water-white product varied in four runs from 1.6735 to 1.6799 as compared with 1.6570 for very pure material distilled through a column. Hence, the distillate obtained as described above was 95 to 97% pure. The impurity is arsenic trichloride (*d* 2.163), the boiling point of which is 20° below that of ethyldichloroarsine. Fractionation through a column readily separared the two substances. The percentages thus obtained check well with the composition calculated from the density of the crude material.

The material collected in the cold-trap (*ca.* 225 g.) boiled at 12°; it was ethyl chloride.

Anal. Calc'd for C_2H_5Cl: Mol. wt., 64.5. Found: Mol. wt., 65.1.

The solid residue remaining in the reaction flask was nearly pure lead chloride.

Anal. Calc'd for $PbCl_2$: Cl, 25.5. Found: Cl, 25.8.

Other experiments related to the preparation of ethyldichloroarsine. An account of some other experiments conducted with arsenic trichloride and tetraethyllead is given because of the light which these experiments throw on the course and mechanism of the reaction. The low-temperature preparation of ethyldichloroarsine described below is not recommended as a preparative method.

Tetraethyllead (54 g., 0.167 mole) was added to a well-stirred solution of 91.5 g. (0.5 mole) of arsenic trichloride in 235 cc. of carbon tetrachloride. The reaction began at the end of 1.5 hours. The mixture was stirred continuously for about 12 hours at room temperature. The solid reaction product was then collected and the filtrate concentrated to remove the solvent. The residue was distilled through a two-foot Fenske column. Unchanged arsenic trichloride (11 g., b.p. 61.5–63° at 75 mm.) and ethyldichloroarsine (40 g., b.p. 82–83° at 75 mm.) were obtained. This yield of ethyldichloroarsine is 69%, if the first stage reaction is used as a basis of calculation; it is 46%, if the over-all reaction is used. Similar results were obtained when benzene or ligroin were used as solvents and the reaction carried out at room temperature.

In another experiment the proportion of arsenic trichloride to tetraethyllead was four moles to one. The solvent was benzene, and the reaction was carried out at room temperature. The recovered arsenic trichloride amounted to 1.3 mole equivalents; the ethyldichloroarsine obtained was equivalent to 2 moles of arsenic trichloride. These results show that at room temperature, a large excess of arsenic trichloride removed only two ethyl groups from the tetraethyllead.

When an equimolecular mixture of diethyllead dichloride and arsenic trichloride was heated to 125°, there was a vigorous reaction and a gas, presumbaly ethyl chloride, was evolved. The reaction mixture was distilled at 75 mm. The product obtained was ethyldichloroarsine (yield 75%); it boiled at 148–152° when distilled at atmospheric pressure.

Preparation of ethylarsenious oxide. Ethylarsenious oxide was prepared from ethyldichloroarsine by the method of Steinkopf and Mieg (2). An 80% yield of colorless liquid

was obtained (b.p. 158°/10 mm.). The molecular weight of this substance was found to be 376 by the cryoscopic method in benzene [calc'd for $(C_2H_5AsO)_2$, 360].

Preparation of diethylchloroarsine. Ethyldichloroarsine, 52.5 g. (0.3 mole) was heated to 120°, and 48.5 g. (0.15 mole) of tetraethyllead was slowly added. The separation of a white precipitate indicated that a reaction had occurred. After the mixture had been kept at 120° for two hours, the product was distilled directly from the reaction flask. The 39.3 g. of diethylchloroarsine obtained, boiled at 74–78°/74 mm.; d_{20}^{20} 1.215.

Anal. Calc'd for $C_4H_{10}AsCl$: Cl, 21.1. Found: Cl, 18.0.

The product is, therefore, diethylchloroarsine contaminated with a small amount of triethylarsine. It is quite unstable; on contact with air it immediately forms a white solid.

The white residue from the reaction was washed with benzene; it weighed 49 g. Assuming this substance to be diethyllead dichloride, the theoretical yield is 50.5 g.

Anal. Calc'd for $C_4H_{10}Cl_2Pb$: Cl, 21.2. Found: Cl, 21.9.

Preparation of ethyldichlorophosphine. Phosphorus trichloride (137 g., 1 mole) was placed in a 500-ml. three-necked flask fitted with a dropping-funnel with a side-arm through which gas could be introduced, a mechanical stirrer, and a reflux condenser. While a slow stream of nitrogen was passed into the flask, tetraethyllead (100 g., 0.3 mole) was added to the stirred reaction mixture. The reaction was slow; no precipitation of lead chloride occurred until the mixture had been refluxed for two hours. The reaction mixture was heated in an oil-bath kept at 110° until refluxing ceased (about 30 hours). The volatile material was then distilled directly from the reaction vessel. A colorless, evil-smelling distillate was collected (b.p. 113–116°/760 mm.). The yield was never lower than 117 g., 89% of the theoretical. In one experiment a yield of 96% was obtained.

Ethyldichlorophosphine, on exposure to air, rapidly forms a yellow solid. The reaction with air can be minimized by dissolving it in a suitable solvent (*e.g.*, benzene).

Preparation of ethyldichlorostibine. In the apparatus described for the preparation of ethyldichlorophosphine, 68.4 g. (0.3 mole) of dried and pulverized antimony trichloride was suspended in 160 cc. of benzene. Tetraethyllead (32.3 g., 0.1 mole) was then added slowly. The mixture was heated under reflux for 8 hours and then allowed to stand overnight. After the benzene had been removed by distillation, the residue was distilled under reduced pressure. The product which boiled between 113° and 120° at 25 mm. was redistilled. A total of 48.6 g. (71%) of a colorless liquid was obtained (b.p. 62–83° at 1 mm.; *d* 2.182). No fraction with a sharp boiling point could be obtained.

Anal. Calc'd for $C_2H_5Cl_2Sb$: Cl, 31.9. Found: Cl, 31.4.

SUMMARY

The method of preparing ethyldichloroarsine, ethyldichlorophosphine, ethyldichlorostibine, and diethylchloroarsine from tetraethyllead and arsenic trichloride, phosphorus trichloride, antimony trichloride, and ethyldichloroarsine is described.

CHICAGO 37, ILL.

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[Contribution from the Lederle Laboratories Division, American Cyanamid Company]

7-DEHYDROCHOLESTEROL[1]

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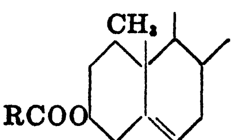
In 1942, Ziegler and co-workers (1), in their classical paper on substitution in the "allylic" position with N-bromosuccinimide, mentioned that cholesteryl esters (I) had been brominated in a similar manner. Although no details were given, it was to be inferred that a dehydrobromination had also been carried out to give the desired 7-dehydrocholesteryl esters (III). This represented a novel method of preparing 7-dehydrocholesterol. The publication on this process mentioned by the German workers as being forthcoming, has not appeared. This undoubtedly may be ascribed to conditions created by the war.

Subsequently, several laboratories have undertaken a study of this novel preparation of 7-dehydrocholesterol (IV), and many publications have appeared on this subject (2–7).

We have been working on this synthesis independently and wish at this time to present a detailed account of our results.

The synthesis may be represented as follows:



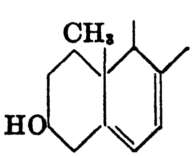
$\xrightarrow{\text{Bromination}}$ "Bromocholesteryl" Ester

I — II

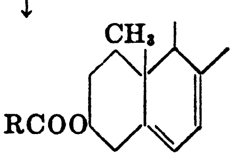
Ia R = CH_3 Cholesteryl acetate
Ib R = C_6H_5 Cholesteryl benzoate
Ic R = $(NO_2)_2C_6H_3$ Cholesteryl 3,5-dinitrobenzoate

IIa "Bromocholesteryl" acetate
IIb "Bromocholesteryl" benzoate
IIc "Bromocholesteryl" 3,5-dinitrobenzoate

↓ Dehydrobromination



$\xleftarrow{\text{Hydrolysis}}$



IV — III

7-Dehydrocholesterol

IIIa 7-Dehydrocholesteryl acetate
IIIb 7-Dehydrocholesteryl benzoate
IIIc 7-Dehydrocholesteryl 3,5-dinitrobenzoate

[1] Presented before the Division of Organic Chemistry at the 114th meeting of the American Chemical Society, Washington, D. C., August 30–September 2, 1948.

[2] Present address: William R. Warner and Company, New York, N. Y.

[3] Deceased, August 9, 1948.

The discussion of the preparation may be conveniently divided into three parts; (A), bromination; (B), dehydrobromination; and, (C), isolation and estimation of yields.

A. BROMINATION

A systematic study of reaction conditions showed that the bromination with N-bromosuccinimide or N-bromophthalimide was affected by a number of factors: mole ratio of NBS[4] to cholesteryl ester, type and boiling point of solvent and presence of catalysts, *e.g.* light. This work was done primarily on three esters of cholesterol, *i.e.* the acetate (Ia), benzoate (Ib) and 3,5-dinitrobenzoate (Ic), and of these three our attention has been concentrated on the benzoate. Remarks concerning the benzoate throughout the discussion will, for the most part, be true of the other two esters.

Our experience has shown that a 20% excess of NBS led to the best yields. Others (*loc. cit.*) have used varying mole ratios, varying from 0.8 to 1.5 equivalents of NBS. Results indicated that use of less than one equivalent of NBS led to difficulties in the isolation of the final product, due to the presence of unreacted cholesteryl ester, whereas use of more than 1.2 equivalents gave lower yields (see Tables II and III).

The time of bromination depends on the solvent and catalyst used. It was definitely demonstrated that the boiling point of the solvent and consequently the temperature at which the reaction was run, determines the bromination time. When the reaction was done in carbon tetrachloride (see Table II) the bromination time was of the order of ten minutes, whereas if a catalyst was present the reaction time could be reduced to, at the most, two minutes. [1.5 minutes with petroleum ether (see Table III).] It was found that the reaction could be catalyzed by irradiation of varying wavelengths.[5] The most convenient light was generated by photospot lamps.

When the bromination was carried out in petroleum ether, b.p. 64–66°, with visible irradiation the yield was higher than when carried out in carbon tetrachloride under the same conditions. Others (*loc. cit.*) have used ether, petroleum ether of various boiling ranges, ethyl acetate, and carbon tetrachloride for this purpose.

The boiling point of the petroleum ether used played an important role in the time of bromination and the final yield of product. An examination of Table IV indicates that with the lower-boiling petroleum ethers, at least twenty minutes are required for sufficient bromination to obtain good yields. It should be pointed out that more extended times may increase the yields in these cases. Use of higher-boiling petroleum ethers tends to decrease the yield, *i.e.*, the use of petroleum ether b.p. 95–100° gave a crude yield of 16.7% as compared to a crude yield of 41.5% for petroleum ether, b.p. 55–60°.

Several experiments were carried out to determine at what stage in the bro-

[4] NBS = N-Bromosuccinimide

[5] Buisman, Stevens, and v.d. Vliet (5) have made a similar observation and have used ultraviolet light to catalyze the bromination reaction.

mination step the dehydrobrominating agent should be added to obtain the best results. Addition of an organic base such as dimethylaniline to the bromination mixture before reaction completely prevented bromination. It was found that addition of the amine to the refluxing bromination mixture immediately after complete reaction rather than waiting until after separation of the succinimide increased the yield by several per cent.

Mention should be made of the purity of the cholesteryl ester used in the bromination. It was found, especially in the case of the benzoate, that the ester must be extremely pure to give the maximum yield. This appeared to pertain less in the case of the acetate. The necessity for the absolutely pure benzoate is not well understood. Perhaps the answer lies in the possibility that traces of pyridine remaining from the benzoylation interfere. The adverse affect of amines on the bromination reaction has been discussed above.

B. DEHYDROBROMINATION

The yield in the dehydrobromination step was dependent on several factors: type and purity of dehydrobrominating agent, and presence or absence of a solvent. In our early work, dehydrobromination was done with no solvent other than the amine. Investigation showed that the use of an inert solvent as a diluent greatly facilitated this step and increased the yield. Examination of Tables II and III shows that *s*-collidine in xylene was the best combination of those tried. Several combinations used, such as pyridine in toluene, are not reported in the tables. Other workers (*loc. cit.*)[6] have carried out this step without a diluent.

The use of a solvent greatly facilitated the work-up of the product. It was a simple matter to separate the amine hydrobromide and evaporate the diluent *in vacuo* to give the crude product.[7]

The purity of the amine had a bearing on the final yield. Highly purified *s*-collidine gave a slightly better yield than the material used as received.[8]

C. ISOLATION, ESTIMATION OF YIELDS

The crude 7-dehydrocholesteryl ester (III) was examined spectroscopically and, in this manner, a "crude" yield was obtained. The purity of the ester was determined by an estimation of the molecular extinction coefficient at the 282 mμ maximum. This method was found to be fairly reliable only when the 282 mμ maximum was equal to or higher than the 272 mμ maximum. Estimation of the purity of the product by this method is, we feel, open to a good deal of criti-

[6] Buisman, Stevens, and v.d. Vliet (5) have reported one experiment with cholesteryl acetate where the dehydrobromination was carried out with *s*-collidine in xylene in the presence of calcium carbonate.

[7] Removal of excess amine by steam distillation or work-up by extraction afforded no real advantage, in the case of the benzoate, over the process herein outlined. Although a purer "crude" product was obtained, the over-all yield was not appreciably affected. Extraction work-up, however, was preferred for the acetate.

[8] A similar observation has been reported by N. V. Philips' Gloeilampenfabriken in British Patent Application 30908 (November 21, 1947).

cism; however, aside from isolation of the pure product, it is the only convenient way to determine the yield.

In many cases, pure 7-dehydrocholesteryl acetate (IIIa) or benzoate (IIIb) were isolated and, in this manner, the over-all yield could be accurately determined. It is felt that the high yields claimed by others are, in many cases, due to estimation of only the 282 mμ maximum without consideration of the effect of impurities on the absorption curve.

Since most of the experiments were carried out in a standard manner, isolation of the pure ester in several instances served as a check on the spectroscopic assay of the crude product. In eight out of the nine cases reported here (Tables II, III, and IV) where both "crude" and pure yields are given, the average difference between the two yields is 8.1%. It is reasonable to assume that purification losses are of this order of magnitude, and, therefore, the spectroscopic assays reported in the tables are reasonably reliable. In the ninth case (Run 13, Table III), where a discrepancy of 20% is reported, it may be said with certainty that the crude yield of 46.2% is in error.

By variation of reaction conditions, yields of over 40% (based on spectrophotometric assay of the crude product) have been obtained when the benzoate was used. Several recrystallizations from acetone gave a 30% yield of pure 7-dehydrocholesteryl benzoate (IIIb). Under similar conditions a 31% yield of crude 7-dehydrocholesteryl acetate (IIIa) was obtained; pure 7-dehydrocholesteryl acetate (IIIa) was isolated in 24% yield.

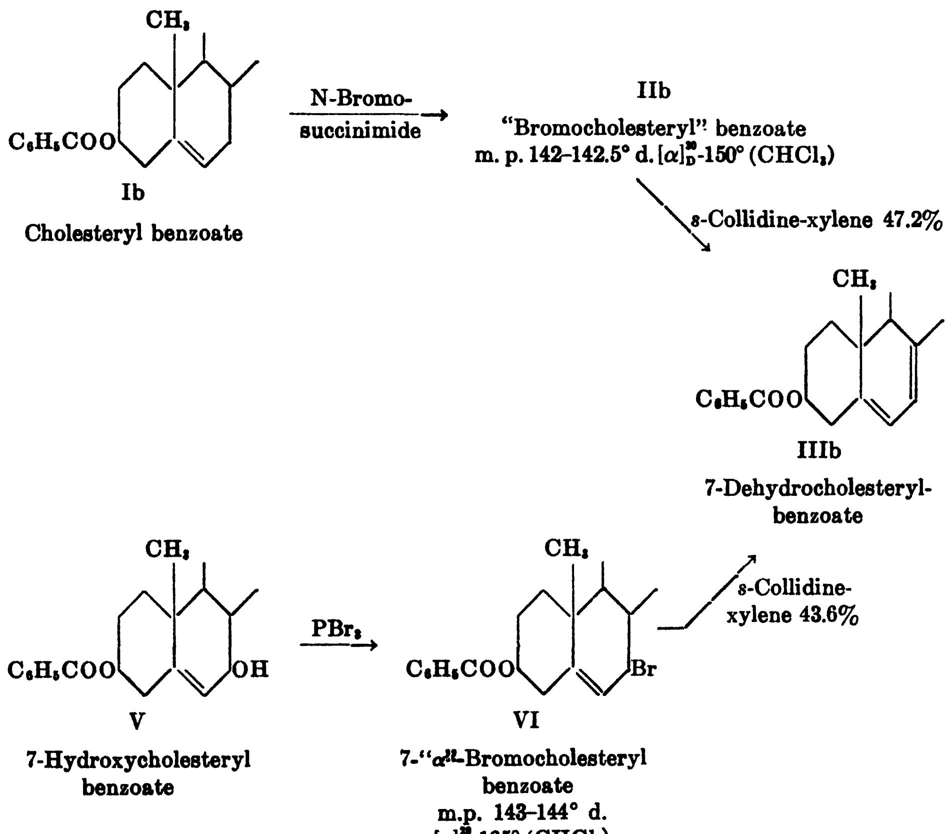
In earlier work we isolated pure 7-dehydrocholesteryl 3,5-dinitrobenzoate (IIIc) in 4.7% yield, but later process improvements should allow a considerable increase in that figure.

The Dutch workers (5) are the only investigators who previously have reported the isolation of a pure 7-dehydrocholesteryl ester directly from the dehydrobromination mixture by simple crystallization. These workers claimed a 29% yield of crude 7-dehydrocholesteryl acetate (IIIa), the melting point and spectrum of which were not stated, nor was the yield of the pure ester given. They also report in a footnote that yields of over 40% have been obtained, but no details have been reported.

The pure 7-dehydrocholesteryl esters, acetate (IIIa), benzoate (IIIb), and 3,5-dinitrobenzoate (IIIc) obtained by the N-bromosuccinimide synthesis were hydrolyzed by alcoholic potash in the usual manner to give pure 7-dehydrocholesterol (IV) which was characterized by melting point, optical rotation and ultraviolet absorption spectrum. In turn 7-dehydrocholesterol (IV) was converted to its acetate (IIIa), benzoate (IIIb), dinitrobenzoate (IIIc) and *p*-nitrobenzoate. In Table I are listed the physical properties of 7-dehydrocholesterol (IV) and the above four esters.

It will be noticed in the process outlined above that the intermediate "bromocholesteryl" benzoate (IIb) was not isolated. Experience has shown that the less it is handled, the better the yield. However, we have concerned ourselves with the isolation and characterization of this intermediate. This product has been isolated, m.p. 142.0–142.5°d., $[\alpha]_D^{30}$ − 150° ($CHCl_3$). 7-"α"-Bromocholes-

teryl benzoate (VI) (the assignment of configuration is arbitrary) prepared from 7-hydroxycholesteryl benzoate (V) (8) and phosphorus tribromide melted at 143–144° d., $[\alpha]_D^{20}$ − 165° ($CHCl_3$).[9] A mixed melting point determination showed only a slight depression. However, the difference of 15° in optical rotation is significant and suggests incomplete identity. We believe that "bromocholesteryl" benzoate (IIb) consists primarily of 7-"α"-bromocholesteryl benzoate (VI). The nature of the impurity has not been investigated. Both "bromocholesteryl" benzoate (IIb) and 7-"α"-bromocholesteryl benzoate (VI), on treatment with *s*-collidine in xylene gave about the same yield of 7-dehydrocholesteryl benzoate (IIIb) (47% and 44% respectively).



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[9] Buisman, Stevens, and v.d. Vliet (5) give as the melting point of 7-"α"-bromocholesteryl benzoate (VI), 139–140°, gas bubbles in the melt at 141°. For 7-"β"-bromocholesteryl benzoate they give the crude melting point of 132–133°, bubbles above the melting point. No melting point is given for the recrystallized material. The melting point of the crude bromo-compound which they isolated from the reaction mixture was 135–136°, bubbles at 138°.

Redel and Gauthier (7) report the intermediate "bromocholesteryl" benzoate (IIb) to have the melting point 135–137° d., $[\alpha]_D^{18}$ −173° ($CHCl_3$).

In one experiment with cholesteryl 3,5-dinitrobenzoate (Ic) the brominated product was isolated. However this intermediate has not been well characterized. Further work on this compound was abandoned in favor of more promising work on the benzoate.

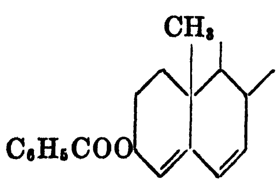
When the isolated "bromocholesteryl" benzoate (IIb) was dehydrobrominated it was possible, after separation of the 7-dehydrocholesteryl benzoate, to isolate another product[10] which melted at 125.5–126.5°, $[\alpha]_D^{28}$ – 90.7° ($CHCl_3$), absorption maxima at 239 and 279–281 mμ, ϵ_{239} = 38,200, ϵ_{279-81} = 1,100. These properties agree best with those of $\Delta^{4,6}$-cholestadienyl benzoate as described by Spring and Swain (9), m.p. 128–129°, $[\alpha]_D^{21}$ –81° ($CHCl_3$), single maximum at 239 mμ,

TABLE I

PHYSICAL CONSTANTS OF 7-DEHYDROCHOLESTEROL AND ITS ESTERS

COMPOUND	M.P. °C	$[\alpha]_D$ ($CHCl_3$)	PRINCIPAL U.V. ABSORPTION MAXIMA WITH MOLECULAR EXTINCTION COEFFICIENTS
7-Dehydrocholesterol	145–147.5 149–151.5	–120°	ϵ_{272} = 10,800, ϵ_{282} = 11,570, ϵ_{292} = 6,510 ϵ_{272} = 11,250, ϵ_{282} = 11,900, ϵ_{293} = 6,650
7-Dehydrocholesteryl acetate	128–130	–77.7°	ϵ_{272} = 10,350, ϵ_{282} = 10,850, ϵ_{294} = 6,140
7-Dehydrocholesteryl benzoate	139–141, 189	–53.1°	ϵ_{272} = 13,270, ϵ_{282} = 13,580, ϵ_{294} = 7,400 ϵ_{272} = 13,360, ϵ_{282} = 13,510, ϵ_{294} = 7,290
7-Dehydrocholesteryl *p*-nitrobenzoate	151–153	–53.9°	ϵ_{271} = 22,940, ϵ_{282} = 19,600
7-Dehydrocholesteryl 3,5-dinitrobenzoate	210.5–212.5d	–42.1°	ϵ_{271} = 15,010, ϵ_{282} = 13,730, ϵ_{293} = 8,270 ϵ_{271} = 14,840, ϵ_{282} = 13,490, ϵ_{293} = 8,020 ϵ_{271} = 16,650, ϵ_{282} = 14,940, ϵ_{293} = 8,750

ϵ = 33,000. It is believed that the by-product isolated by us is most probably $\Delta^{4,6}$-cholestadienyl benzoate (VII) but we have not pursued this feature of the problem further.



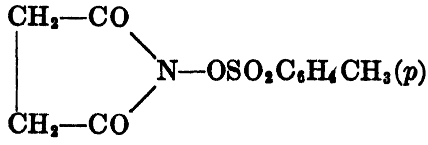
VII

$\Delta^{4,6}$-Cholestadienyl benzoate

[10] Buisman, Stevens, and v.d. Vliet (5) have pointed to the presence of this compound in the reaction mixture and have indicated possible allylic rearrangements to account for its formation.

Redel and Gauthier (7) have isolated it by chromatography, m.p. 125–126°, $[\alpha]_D^{24}$ –84.4°. On hydrolysis they obtained the free sterol which, in turn, was converted to the acetate. Both products were characterized by melting point and rotation.

During the early phases of our work we were interested in the activity of N-tosylsuccinimide (VIII) (10) under similar conditions to NBS and N-bromophthalimide. Mixtures of N-tosylsuccinimide (VIII) with cholesteryl benzoate were refluxed in carbon tetrachloride on the steam bath for 24 hours with and without benzoyl peroxide, and in both cases the starting material was recovered unchanged.



VIII

N-tosylsuccinimide

EXPERIMENTAL

Absorption spectra. All spectra were determined with a Beckmann quartz spectrophotometer (mfg'd. by the National Technical Laboratories, Pasadena, California), and were determined in 1% chloroform-absolute alcohol, *i.e.*, the weighed sample was dissolved in 1 ml. of reagent chloroform and this solution was rapidly diluted to 100 ml. with commercial absolute alcohol.

Melting points. All m.p.'s are uncorrected. When a compound has a cloudy melt, the clearing point is given after the m.p., *e.g.*, 139–141°, 189°. Melting points of the various bromo derivatives were taken by inserting the sample in the bath a few degrees below its m.p.

Yields. All "crude" yields are based on spectroscopic analysis. The value of the molecular extinction coefficient at the 282 mμ absorption maximum was taken as a measure of the purity of the material at hand, and was based on the following standards: 7-dehydroacetate, ϵ_{282} = 10850; 7-dehydrobenzoate, ϵ_{282} = 13500; and 7-dehydro-3,5-dinitrobenzoate ϵ_{282} = 13500.

7-Dehydrocholesteryl acetate (*IIIa*). A mixture of 17.12 g. (0.04 M) of cholesteryl acetate (Ia), 8.56 g. (0.048 M) of NBS (1) and 200 ml. of petroleum ether, b.p. 64–66°, (purified with conc'd sulfuric acid and potassium permanganate[11]) was heated to reflux with two photospot lamps (General Electric Co., RSP-2, 115 v) and was refluxed for 4 minutes with the lamps as the only source of heat. Eight ml. of *s*-collidine was then added to the refluxing mixture, which was cooled and filtered. The filtrate was evaporated *in vacuo* (nitrogen atmosphere); the distillation temperature was maintained at room-temperature and below. The residue was treated with about half of 100 ml. of xylene containing 4 ml. of *s*-collidine and the distillation was continued for a short time to ensure removal of traces of petroleum ether. The remainder of the *s*-collidine-xylene solution was added, the mixture was refluxed for 15 minutes (nitrogen atmosphere), cooled, and treated with water. The product was worked up in xylene and the extract was washed successively with cold, very dilute hydrochloric acid, water, sodium bicarbonate solution, and water. The extract was dried with magnesium sulfate, treated with Norit and filtered through Celite. Evaporation of the brown-yellow filtrate gave an oily solid which was dissolved in acetone. The solution was put under a nitrogen atmosphere and cooled. The crystals which separated were collected and washed with a small amount of cold acetone and a small amount of methanol; white solid intermixed with a very small amount of oily solid, wt. 5.78 g.; m.p. 114–123.5°; ϵ_{282} = 9860 (90.8% pure); 30.8% yield. The crude 7-dehydroacetate was recrystallized twice from acetone-methanol, wt. 4.14 g.; m.p. 128–129.5°; 24.4% yield.

[11] All petroleum ethers used were similarly purified.

In another run with 4.28 g. (0.01 M) of cholesteryl acetate, 2.14 g. (0.012 M) of NBS and 50 ml. of petroleum ether, b.p. 64–66°, there was obtained 1.48 g.; m.p. 118–123°; ϵ_{282} = 10320 (95.2% pure); 33% yield.

7-Dehydrocholesteryl benzoate (IIIb). A. A mixture of 19.6 g. (0.04 M) of cholesteryl benzoate, 8.55 g. (0.048 M) of NBS, and 200 ml. of petroleum ether, b.p. 64–66°, was refluxed for 4 minutes by the light and heat of two RSP-2 photospot lamps, placed two inches from the reaction vessel. Eight ml. of *s*-collidine was added to the boiling solution which was cooled, filtered with suction to remove succinimide, and distilled *in vacuo* at −10 to +10° to remove the petroleum ether. A dark red oil containing *s*-collidine and the crude "bromocholesteryl" benzoate remained in the flask.

TABLE II

CHOLESTERYL BENZOATE → 7-DEHYDROCHOLESTERYL BENZOATE

Bromination Solvent: CCl_4

	CB MOLES	NBS MOLES	BROMINATION TIME OF REFLUX MINUTES	IRRADIATION BROMINATION	STRIPPING AGENT—SOLVENT	STRIPPING TIME OF REFLUX MINUTES	CRUDE YIELD, %	PURE YIELD, %
1	0.01	0.01	10	—	DMA-T	30	11.2	—
2	.01	.011	10	—	DMA-T	30	18.8	11.3
3	.01	.012	10	—	DMA-T	30	22.6	—
4	.01	.0125	10	—	DMA-T	30	17.3	13.1
5	.04	.048	2	V-1	DMA-T	30	27.0	18.3
6	.01	.012	3	PF	DMA-T	30	23.4	17.2
7	.01	.012	2	U.V.	DMA-X	10	25.6	—
8	.01	.012	2	I.R.	DMA-X	10	26.4	—
9	.04	.048	2	V-2	DMA-X	10	28.2	21.5
10	.01	.012	2	V-2	C-X	15	32.0	—

CB = Cholesteryl benzoate
NBS = N-Bromosuccinimide
V-1, V-2 = One and two, resp., photospot lamps; type RSP-2, 115 v, General Electric Co.
U.V. = Ultraviolet lamp; type 16200, 115 v, 125 w, Hanovia Chemical and Mfg. Co.
I.R. = Infra-red lamp; type R-40, 115 v, 250 w, Westinghouse Electric Co.
P.F. = Photoflood lamp; type 2A, General Electric Co.
DMA = Dimethylaniline
C = *s*-Collidine
T = Toluene
X = Xylene
p.e. = petroleum ether

The oil was dissolved in a mixture of 100 ml. of xylene, b.p. 138–142° and 4 ml. *s*-collidine, refluxed in a nitrogen atmosphere for 15 minutes, and cooled; anhydrous magnesium sulfate was added, the slurry was filtered with suction, and the filtrate was distilled *in vacuo*. The partially crystalline red oil was treated with 100 ml. of acetone and cooled in an ice-bath, wt. 12.48 g.; m.p. 122–128°; 152° ϵ_{282} = 8700 (64.5% pure); 41.3% "crude" yield. After four recrystallizations from acetone there remained 5.08 g., m.p. 138–140.5°, 187.5° and an additional 0.84 g., m.p. 138–140.5°, 185.5° was obtained from the mother liquors. The overall yield was 30.3%.

B. Numerous experiments (*ca.* 100) with cholesteryl benzoate were performed; a portion of these are reported in Tables II, III, and IV. All the experiments were carried out essentially as under (*A*).

7-Dehydrocholesteryl 3,5-dinitrobenzoate (IIIc). A. Five and eight-tenths grams

TABLE III

CHOLESTERYL BENZOATE → 7-DEHYDROCHOLESTERYL BENZOATE

Bromination Solvent: Petroleum Ether, bp. 64–66°

	CB MOLES	NBS MOLES	BROMINATION TIME OF REFLU MINUTES	IRRADIATION BROMINATION	STRIPPING AGENT—SOLVENT	STRIPPING TIME OF REFLUX MINUTES	CRUDE YIELD, %	PURE YIELD, %
1	0.01	0.0115	4	V-1	DMA-T	30	22.8	—
2	.01	.012	4	V-1	DMA-T	30	25.2	14.1
3	.01	.013	4	V-1	DMA-T	30	24.7	—
4	.01	.012	4	V-2	DMA-X	12	30.9	—
5	.01	.01175	4	V-2	C-X	15	37.0	—
6	.01	.012	1.5	V-2	C-X	15	36.6	—
7	.01	.012	2	V-2	C-X	15	39.0	—
8	.01	.012	2.5	V-2	C-X	15	36.8	—
9	.01	.012	3	V-2	C-X	15	38.1	—
10	.01	.012	3.5	V-2	C-X	15	36.4	—
11	.01	.012	4	V-2	C-X	15	37.2	—
12	.04	.048	4	V-2	C-X	15	41.3	30.3
13	.04	.048	4	V-2	C-X	15	46.2	26.2
14	.01	.012	4	V-2	C-X	15	42.7	—
15	.01	.01225	4	V-2	C-X	15	37.6	—
16	.01	.013	4	V-2	C-X	15	34.7	—

See legend to Table II.

TABLE IV

CHOLESTERYL BENZOATE → 7-DEHYDROCHOLESTERYL BENZOATE

Irradiation Bromination: V-2, 0.01 *M* C.B. 0.012 *M* N.B.S.

	BROMINATION SOLVENT	BROMINATION TIME OF REFLUX MINUTES	CRUDE YIELD, %	PURE YIELD, %
1	p.e. 45°	20	32.2	—
2	p.e. 50–55°	20	33.6	—
3	p.e. 55–60°	20	39.7	—
4	p.e. 55–60°	30	41.5	31.8
5	p.e. 60–65°	20	38.3	—
6	p.e. 65–70°	4	37.2	—
7	p.e. 70–75°	4	35.2	—
8	p.e. 75–80°	4	34.4	—
9	p.e. 85–90°	4	20.4	—
10	p.e. 90–95°	4	24.6	—
11	p.e. 95–100°	4	16.7	—

See legend to Table II.

(0.01 M) of cholesteryl 3,5-dinitrobenzoate was dissolved in 100 ml. of carbon tetrachloride by heating on the steam-bath. One and six-tenths grams (0.009 M) of NBS was added; the mixture was refluxed for 25 minutes, cooled, and filtered. The filtrate was concentrated *in vacuo*. This gave a yellow solid which was dissolved in 60 ml. of toluene, treated with 0.79 g. (0.01 M) of pyridine, and was refluxed for 2 hours in a nitrogen atmosphere. The resulting pyridine hydrobromide was removed and the filtrate was evaporated *in vacuo*.

This gave an orange, oily solid which was treated with acetone; the insoluble yellow solid was separated, wt. 0.71 g.; m.p. 176–178° d.; ϵ_{282} = 4900. Three recrystallizations from benzene-acetone gave 258 mg. of pure 7-dehydro-dinitrobenzoate, m.p. 210–212° d. From the mother liquor 91 mg. more of product was obtained, m.p. 206.5–208° d.; 6.7% yield (based on NBS).

B. A mixture of 2.9 g. (0.005 M) of cholesteryl 3,5-dinitrobenzoate, 1.01 g. (0.0045 M) of N-bromophthalimide, and 50 ml. of carbon tetrachloride was reacted as above (*A*) and gave 90 mg. of 7-dehydro-dinitrobenzoate, m.p. 207–209.5° d.; 3.5% yield.

C. A mixture of 23.2 g. (0.04 M) of cholesteryl 3,5-dinitrobenzoate, 7.12 g. (0.04 M) of NBS, and 250 ml. of carbon tetrachloride was refluxed for 12 minutes, cooled and the succinimide was separated, wt. 3.95 g. (calc. wt. 3.96 g.); m.p. 115–122°.

The filtrate was evaporated *in vacuo* and the residue was treated with 10 ml. of dimethylaniline and 150 ml. of toluene. The mixture was refluxed for 0.5 hour. Anhydrous magnesium sulfate was added to the cooled mixture which was filtered through Celite. Evaporation of the toluene gave an oily residue which crystallized on treatment with acetone, wt. 6.3 g.; m.p. 180–182°; ϵ_{282} = 4940 (36.8% pure). Seven recrystallizations from benzene-acetone gave 1.1 g. of pure dinitrobenzoate, m.p. 209–211° d.; 4.7% yield.

D. Twelve and seven-tenths grams (0.025 M) of cholesteryl 3,5-dinitrobenzoate was dissolved in 250 ml. of carbon tetrachloride and treated with 5.15 g. (0.029 M) of NBS. The mixture was refluxed for 15 minutes, cooled, and the succinimide was separated, wt. 2.82 g. (calc. wt. 2.87 g.); m.p. 119–123°.

The yellow filtrate was evaporated *in vacuo*; the residue was treated with 25 ml. of benzene which was removed *in vacuo*. The benzene treatment was repeated. This gave 17 g. of brominated product which was practically all solid. Fractional recrystallization from ether, chloroform-ether and ether-absolute alcohol gave the following fractions: (a) most insoluble, wt. 3.44 g.; needles, m.p. 144–145°, transition, change in color, and final melt at 194–198°, dark melt;

Anal. Calc'd for $C_{34}H_{47}BrN_2O_6$: C, 61.90; H, 7.18; N, 4.25; Br. 12.12.
Found: C, 61.56; H, 7.18; N, 4.07; Br. 13.11.

(b) wt. 1.72 g., m.p. 137–144°, transition, change in color, gradual melt up to about 197°, dark melt; (c) mother liquor evaporated to dryness; (d) wt. 1.8 g., slight yellow tint, m.p. 130–132°, transition in color, final melt at 194°; (e) wt. 1.58 g., m.p. 125–135°, transition, final melt at about 192°; and (f) wt. 7.1 g., most soluble mother liquor evaporated to dryness, multi-colored solid with dark areas.

Three and eight-hundredths grams of Fraction (a) was treated with 0.74 g. of pyridine in 100 ml. of toluene. The mixture was refluxed for two hours in a nitrogen atmosphere, cooled and the pyridine hydrobromide was separated. The filtrate was evaporated to dryness *in vacuo* in a nitrogen atmosphere. The residue was treated with acetone and the insoluble orange solid was collected, wt. 0.38 g.; m.p. 194–201° d.; ϵ_{282} = 12020 (89% pure). Recrystallization from benzene-acetone gave 200 mg. of pure *7-dehydro-dinitrobenzoate*, m.p. 209–210° d.; $[\alpha]_D^{33}$ – 38.9°, $[\alpha]_D^{28.5}$ – 42.3° (24.4 mg., 32.6 mg. in 2 ml. chloroform, 1 dcm. semi-micro tube, gave α_D^{33} – 0.47° and $\alpha_D^{28.5}$ – 0.69° resp.); absorption maxima at 259, 272, 282 and 293.5–294 mμ; ϵ_{259} = 14990, ϵ_{272} = 15160, ϵ_{282} = 13420 and $\epsilon_{293.5-294}$ = 7690.

The middle fractions (Fractions b, c, d, and e) were combined (wt. 6.7 g.), dissolved in 125 ml. of toluene, treated with 1.58 g. of pyridine, and the mixture was refluxed for two hours in a nitrogen atmosphere. The pyridine hydrobromide was removed by filtration and the filtrate was evaporated practically to dryness *in vacuo*. Acetone was added and the resulting solid was collected by filtration, wt. 0.6 g.; m.p. 160–162° d.; ϵ_{282} = 10040 (74% pure). Recrystallization from acetone-benzene gave 0.27 g. of pure *7-dehydro-dinitrobenzoate*, m.p. 209.5–211.5° d.; absorption maxima at 252, 259, 271, 282, and 293 mμ; ϵ_{252} = 15430, ϵ_{259} = 15020, ϵ_{271} = 14840, ϵ_{282} = 13490 and ϵ_{293} = 8020, $[\alpha]_D^{32}$ – 36.3° (34.7 mg. in 2 ml. chloroform, 1 dcm. semi-micro tube, gave α_D^{32} – 0.61°).

The most soluble fraction (f) on similar treatment with pyridine and toluene gave none of the desired 7-dehydro-dinitrobenzoate.

"Bromocholesteryl" benzoate (IIb). A. A mixture of 235.2 g. (0.48 M) of cholesteryl

benzoate, 85.4 g. (0.48 M) of NBS and 2 l. of carbon tetrachloride was refluxed for 15 minutes, cooled and the succinimide was removed by filtration, wt. 46.3 g. (calc'd wt. 47.6 g.); m.p., 120–125°. The filtrate was evaporated *in vacuo* with slight heating, and the red viscous oil so obtained was dissolved in 400 ml. of acetone. The solution was allowed to stand at room temperature overnight, and the crystals which separated were collected by filtration and were washed with acetone, wt. 45.9 g.; m.p. 130–136° d. From the mother liquor two more fractions of crystals were obtained, wt. 98.0 g. and 23.5 g.; m.p. 132–137° d. and 138–141° d. resp.

The first fraction consisted primarily of cholesteryl benzoate. The other two fractions were triangularly recrystallized from petroleum ether (60–80°) and gave 54.1 g. of "bromocholesteryl" benzoate, m.p. 142–143° d.

Anal. Calc'd for $C_{34}H_{49}BrO_2$: Br. 14.03. Found: Br. 14.04.

B. A mixture of 97.5 g. (0.20 M) cholesteryl benzoate, 37.4 g. (0.21 M) NBS and 1 l. of carbon tetrachloride was refluxed on the steam-bath for 3 minutes, cooled and the succinimide was separated, wt. 20.8 g. (calc'd wt. 20.8 g.); m.p. 110–123°.

The filtrate was evaporated *in vacuo* and the residual oil was taken up in ether. Thirty grams of solid separated, m.p. 115–123° d. The mother liquor on working with acetone gave 25.3 g.; m.p. 135–137.5° d. The mother liquor from this fraction gave 5.75 g.; m.p. 130–133° d.

The middle fraction was recrystallized three times from acetone to constant m.p., 142–142.5° d. with previous softening at 140–142°, $[\alpha]_D^{31}$ − 146° (13.3 mg. in 2 ml. chloroform, 1 dcm. semi-micro tube, gave α_D^{31} − 0.97°). The material was recrystallized twice from petroleum ether (b.p. 60–70°), m.p. 142–143° d.; $[\alpha]_D^{30}$ − 150° (16.7 mg. in 2 ml. chloroform, 1 dcm. semi-micro tube, gave α_D^{30} − 1.25°).

Dehydrobromination experiments with "bromocholesteryl" benzoate (IIb). A. A mixture of 2 g. of "bromocholesteryl" benzoate, 1 ml. of dimethylaniline, and 25 ml. of toluene was refluxed in a nitrogen atmosphere for 30 minutes, cooled, treated with anhydrous magnesium sulfate, and filtered through Celite. The filtrate was evaporated *in vacuo* in a nitrogen atmosphere. The residue was dissolved in acetone, the solution was concentrated and cooled. Crude *7-dehydro-benzoate* separated and was collected by filtration, wt. 0.68 g.; m.p. 131–135°, 160.5°; ϵ_{282} = 10150 (75.4% pure). From the mother liquor there was isolated an additional 0.3 g. of product, m.p. 110–114° (23.8% pure); yield 33.7%.

B. This reaction when carried out under the same conditions with *s*-collidine and xylene gave 1.0 g. of crude *7-dehydro-benzoate*, m.p. 133–139°, 171°, ϵ_{282} = 10950 (81.2% pure); 47.2% yield.

7-"α"-Bromocholesteryl benzoate (VI). A. A mixture of 1.9 g. of 7-hydroxycholesteryl benzoate, 0.25 ml. of phosphorus tribromide, and 50 ml. of benzene was heated to about 50° three times in four hours. Water was added and the benzene extract was washed with water until a negative Congo Red test was obtained, washed twice with saturated saline solution, dried with magnesium sulfate, filtered and distilled *in vacuo*.

The residue was recrystallized four times from petroleum ether, m.p. 143–144° d.; $[\alpha]_D^{30}$ −165° ($CHCl_3$) (12.7 mg. in 2 ml. chloroform, 1 dcm. semi-micro tube, gave α_D^{30} −1.05°). A mixed melting point with another sample prepared from the reaction of NBS and cholesteryl benzoate gave only slight depression, m.p. 139.5–141.5° d.

Anal. Calc'd for $C_{34}H_{49}BrO_2$: C, 71.86; H, 8.67; Br, 14.03.

Found: C, 71.49, 71.51; H, 9.07, 9.10; Br, 14.48, 13.78.

Recrystallization of the bromo compound was unsatisfactory if the material was allowed to stand in warm acetone for any length of time as decomposition occurred.[13]

B. Seven-tenths of a gram of 7-hydroxycholesteryl benzoate in 20 ml. of benzene was treated with 0.15 ml. of phosphorus tribromide; the mixture was allowed to stand at room temperature for four hours. The product was worked up as in (*A*) and gave 0.45 g. of the desired product, needles, m.p. 143–145° d., bubbles.

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[13] Buisman, Stevens, and v.d. Vliet (5) have made a similar observation.

Dehydrobromination of 7-"α"-bromocholesteryl benzoate (VI). A. Three-tenths of a gram of the 7-"α"-bromo-benzoate was refluxed with 0.2 ml. of dimethylaniline in 15 ml. of toluene for 0.5 hour (nitrogen atmosphere), cooled, filtered through Celite and distilled *in vacuo*. Recrystallization from acetone gave pure *7-dehydro-benzoate*, m.p. 139.5–141°, 188.5°; ϵ_{272} = 12750, ϵ_{282} = 13000, ϵ_{294} = 7200.

B. 7-"α"-Bromo-benzoate (0.45 g.) was refluxed for 20 minutes with 0.5 ml. of s-collidine in 20 ml. of xylene (nitrogen atmosphere), and the product was worked up in the usual manner. This gave 0.25 g. of *7-dehydro-benzoate*, m.p. 131–135°, 162°; ϵ_{282} = 9150 (67.7% pure); 43.6% yield.

7-Dehydrocholesterol (IV).[13] A mixture of 7.5 g. of pure 7-dehydrocholesteryl benzoate (prepared by the N-bromosuccinimide method) and 150 ml. of filtered 5% alcoholic potash was refluxed on the steam-bath for one hour in a nitrogen atmosphere. The mixture was cooled in an ice-bath; the resulting crystals were filtered and washed with cold alcohol, water, and alcohol. During this operation crystals separated in the filtrate. They were combined with the main batch of crystals. Recrystallization from acetone gave 4.5 g., m.p. 142–145° (dried over Drierite). More material was isolated from the mother liquors. An aliquot was further recrystallized from acetone, m.p. 145–147.5°; $[\alpha]_D^{20.5}$ −120° (14 mg. in 2 ml. of chloroform, 1 dcm. semi-micro tube, gave $\alpha_D^{20.5}$ −0.84°).

In another hydrolysis the initially isolated *dehydrocholesterol* melted at 145–148° (dried 2 hours *in vacuo*, oil pump); absorption maxima at 272, 282 and 294 mμ, ϵ_{272} = 9500, ϵ_{282} = 10000 and ϵ_{294} = 5700. Recrystallization from acetone gave m.p. 148–151°, ϵ_{272} = 10800, ϵ_{282} = 11570 and ϵ_{293} = 6510. The material was further recrystallized from acetone, m.p. 149–151.5°, ϵ_{272} = 11250, ϵ_{282} = 11900 and ϵ_{293} = 6650. However, one more recrystallization lowered the melting point and extinction coefficients, m.p. 147–148°, ϵ_{272} = 10500, ϵ_{282} = 10660 and ϵ_{293} = 6030.

7-Dehydrocholesterol was converted into the following derivatives in the usual manner. These compounds were recrystallized to constant melting point, optical rotation and absorption spectrum.

(a) *Acetate,*[14] m.p. 128–130°; $[\alpha]_D^{20.5}$ −77.7°, ($CHCl_3$), absorption maxima at 272, 282 and 294 mμ, ϵ_{272} = 10350, ϵ_{282} = 10850 and ϵ_{294} = 6140.

(b) *Benzoate,*[15] m.p. 139–141°, 189°; $[\alpha]_D^{20}$ −53.1° ($CHCl_3$); absorption maxima at 272, 282 and 294 mμ, ϵ_{272} = 13270, ϵ_{282} = 13580 and ϵ_{294} = 7400.

(c) *p-Nitrobenzoate,*[16] m.p. 151–153° (cloudy melt); $[\alpha]_D^{20}$ −53.9° ($CHCl_3$); absorption maxima at 271 and 281 mμ, ϵ_{271} = 22940 and ϵ_{281} = 19600.

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[13] (a) Windaus, Lettré, and Schenck, *Ann.*, **520**, 98 (1935); m.p. 142–143.5°; $[\alpha]_D^{20}$ −113.6 ($CHCl_3$).
(b) Boer, *et al.*, *Konikl. Akad. Wetenschap. Amsterdam*, **39**, 672 (1936); m.p. 149–150°; $[\alpha]_D$ −122.5° (C_6H_6).
(c) Wintersteiner and Ruigh, *J. Am. Chem. Soc.*, **64**, 1177 (1942); m.p. 142.5–143.5°; $[\alpha]_D^{25}$ −121° ($CHCl_3$); ϵ_{282} = 11100.

[14] (a) Schenck, *et al.*, *Ber.*, **69**, 2696 (1936); m.p. 130°.
(b) Windaus and Bock, *Z. physiol. Chem.*, **245**, 168 (1937); m.p. 130°; $[\alpha]_D$ − 84.9° (C_6H_6).
(c) Bernstein, Hicks, Clark, and Wallis, *J. Org. Chem.*. **11**, 646 (1946), predicted a rotation of −77.6° ($CHCl_3$) for 7-dehydro-acetate.
(d) Buisman, Stevens, and v.d. Vliet, *Rec. trav. chim.*, **66**, 87 (1947); m.p. 130.0–130.5°, $[\alpha]_D^{21.5}$ −87° (C_6H_6).

[15] (a) Windaus, Lettré, and Schenck, *Ann.*, **520**, 98 (1935); m.p. 139–140°, 183°; $[\alpha]_D^{20}$ −53.2° ($CHCl_3$).
(b) Buisman, Stevens, and v.d. Vliet (5), m.p. 140–141°, 189°; $[\alpha]_D^{19}$ −55° ($CHCl_3$).

[16] Huber, *et al.*, *J. Am. Chem. Soc.*, **67**, 609 (1945); m.p. 153–154°; $[\alpha]_D$ −49.8° ($CHCl_3$); absorption maxima at ca. 271 and 281 mμ, ϵ_{271} = ca. 23000, and ϵ_{281} = *ca.* 19500 (estimated from curve, values not given).

(d) *Dinitrobenzoate*,[17] m.p. 210.5–212.5° d.; $[\alpha]_D^{30}$ −42.1° ($CHCl_3$); absorption maxima at 252, 260, 271, 282 and 293 mμ, plateau at 230–231 mμ, ϵ_{230-1} = 23650, ϵ_{252} = 16320, ϵ_{260} = 15950, ϵ_{271} = 16650, ϵ_{282} = 14940, and ϵ_{293} = 8750.

$\Delta^{4,6}$-*Cholestadienyl benzoate (VII)* (?).[18] Fifteen and seventeen-hundredths grams, m.p. 139–141.5° d. (Found Br, 14.00), of "bromocholesteryl" benzoate was treated in the usual manner with 10 ml. of pyridine in 250 ml. of toluene. The crude *7-dehydro-benzoate*, m.p. 114–127.5°, 147° (32.7% pure); wt. 6.67 g.; was recrystallized three times from acetone, wt. 1.21 g., m.p. 138.5–140°, 183°; ϵ_{272} = 13740, ϵ_{282} = 13800 and ϵ_{294} = 7350.

From the mother liquors by a triangular recrystallization from acetone the following fractions were obtained: (a) most insoluble m.p. 122–124°, wt. 1.75 g.; (b) m.p. 117–120°, wt. 1.75 g.; ϵ_{240} = 42500, ϵ_{281} = 2800; (c) m.p. 122–124°, 2.52 g.; ϵ_{240} = 36000 and ϵ_{281} = 1680 and (d) mother liquor which was discarded.

Fractions (b) and (c) were combined and recrystallized from acetone to constant melting point, m.p. 124.5–126.5°, ϵ_{239} = 38200 and ϵ_{279-81} = 1100, $[\alpha]_D^{28}$ −90.7° (20.5 mg. in 2 ml. chloroform, 1 dcm. semi-micro tube, gave α_D^{28} −0.93°).

Anal. Calc'd for $C_{34}H_{48}O_2$: C, 83.55; H, 9.90.
Found: C, 83.54; H, 9.88.

Acknowledgment. We are indebted to Messrs. Louis M. Brancone, Oscar Dike, Sanford Aronovic, Kurt Altmann, and Samuel M. Modes for the microanalytical data. Also we wish to thank Mrs. Anna de Grunigen for some of the absorption data.

Addendum. While this manuscript was in process of publication there appeared a series of papers on 7-dehydrocholesterol and related subjects by a group of English workers, Bide, *et al.*, *J. Chem. Soc.*, 1783, 1788 (1948); and, Henbest and Jones, *J. Chem. Soc.*, 1792, 1798 (1948). A 30% over-all yield of 7-dehydrocholesterol from cholesterol by the Ziegler method was claimed. They have also presented evidence which shows that the product obtained from the bromination of cholesteryl benzoate with N-bromosuccinimide is identical with 7-"β"-bromocholesteryl benzoate. We have subsequently reinvestigated this matter, and confirmed the identity of these two compounds. A detailed report will be included in a forthcoming publication on 7-aminosteroids and related compounds.

SUMMARY

1. The reaction between cholesteryl esters, in particular the benzoate, and N-bromosuccinimide, with subsequent elimination of hydrogen bromide to give 7-dehydrocholesteryl esters has been studied in great detail.

2. A procedure has been developed which gave consistently high yields of the 7-dehydrocholesteryl esters. 7-Dehydrocholesteryl benzoate has been prepared in 41–43% yield (spectroscopic determination on crude material); pure

[17] (a) Windaus, Lettré, and Schenck, *Ann.*, **250**, 98 (1935); m.p. 207°, $[\alpha]_D^{20}$ −45.7° ($CHCl_3$).
(b) Wintersteiner and Ruigh, *J. Am. Chem. Soc.*, **64**, 477 (1942); m.p. 209.5–210.5°, $[\alpha]_D$ −38.3° ($CHCl_3$).
(c) Huber, Ewing, and Kriger, *J. Am. Chem. Soc.*, **67**, 609 (1945); m.p. 210–212°, $[\alpha]_D$ −45.7° ($CHCl_3$).

[18] (a) Spring and Swain, *J. Chem. Soc.*, 320 (1941); m.p. 128–129°, $[\alpha]_D^{21}$ − 81° ($CHCl_3$), absorption maximum at 239 mμ, ϵ_{239} = 33000.
(b) Redel and Gauthier (7), m.p. 125–126°; $[\alpha]_D^{24}$ − 84.4° ($CHCl_3$).

benzoate was isolated in 30% yield. Under similar conditions, 7-dehydrocholesteryl acetate was obtained in crude yields of 31–33%, and in a pure yield of 24%.

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(5) BUISMAN, STEVENS, AND V.D. VLIET, *Rec. trav. chim.*, **66**, 87 (1947).
(6) V.D. VLIET AND STEVENS, U. S. Patent 2,441,091 (May 4, 1948).
(7) REDEL AND GAUTHIER, *Bull. soc. chim.*, (5-6) 607 (May–June, 1948).
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(9) SPRING AND SWAIN, *J. Chem. Soc.*, 320 (1941).
(10) EVANS AND DANE, *J. Am. Chem. Soc.*, **52**, 2531 (1930).

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THE REACTION OF PYRIDONES WITH CHLOROACETIC ACID

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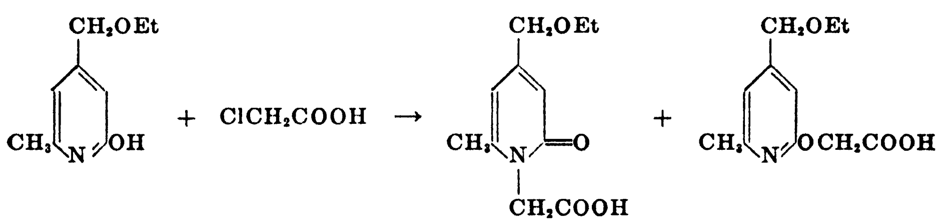
Various investigators have considered the reaction of 2- and 4-pyridones with chloroacetic acid especially in connection with the preparation of X-ray contrast media of the type of Diodrast (1), the diethanolamine salt of 3,5-diiodo-4-pyridone-N-acetic acid, and Rayopake (2), a preparation containing 2-methyl-4,6-dioxo-5-iodotetrahydropyridine-N-acetic acid. To our knowledge only one product has been reported from this type of reaction, namely, that resulting from substitution on the nitrogen atom, although it was recognized that substitution on the oxygen was also possible. In this laboratory we have succeeded in obtaining from the reaction of 4-ethoxymethyl-6-methyl-2-pyridone (I) with chloroacetic acid, two products, which are undoubtedly the N-acetic acid II and the O-acetic acid III. However, we were confronted with the problem of determining which of these two products was to be assigned structure II and which was to be given structure III.

EQUATION A

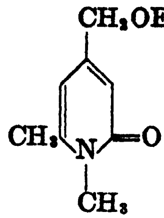


I II III

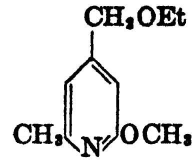
The two products were separated by distillation of their methyl esters. One of the methyl esters came over at a considerably lower temperature. When warmed with hydrochloric acid, the ester group was hydrolyzed to the carboxyl, but nevertheless the resulting compound was sufficiently basic to form a hydrochloride, which could be crystallized from a variety of solvents but not from water.

When the higher-boiling ester was warmed with hydrochloric acid, the ester group was again hydrolyzed, and apparently a hydrochloride was also obtained. However, crystallization from water was sufficient to cause dissociation, so that only the free acid was isolated. When this acid was heated over 200° *in vacuo*, decarboxylation occurred. The analysis indicated that the decarboxylated product could have either structure IV or V, depending on whether the parent acid had structure II or III respectively.

As a logical approach to the problem of assigning correct structures to the above reaction products, an unambiguous synthesis of IV was undertaken. It was early recognized that 1-methyl-3-cyano-4-ethoxymethyl-6-methyl-2-pyridone (VII) might be a suitable starting material for the preparation of IV.



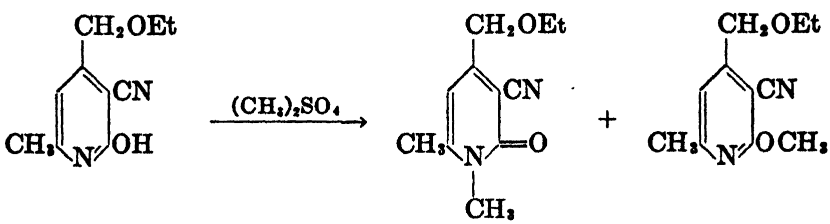
IV



V

Accordingly the methylation of the readily available 3-cyano-4-ethoxymethyl-6-methyl-2-pyridone (VI) was investigated. Treatment with methyl sulfate and alkali gave two compounds, resulting from methylation on the nitrogen atom and on the oxygen atom.

EQUATION B

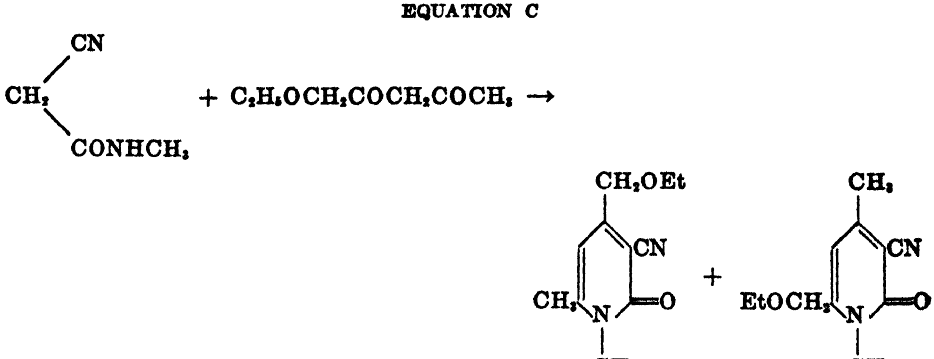


VI VII VIII

Again we were confronted with the problem of ascertaining which of these two compounds was to be assigned the structure VII and which was to be assigned structure VIII.

Fortunately, this latter problem was solved by a consideration of the reaction of cyanoacetmethylamide with ethoxyacetylacetone in the presence of piperidine. As pointed out by Bardhan (3) and investigated by us (4, 5) this type of reaction can occur by two different routes to give two different products. In agreement with this proposition two different compounds were actually isolated. To one of these products must be assigned the structure VII and to the other structure IX.

EQUATION C

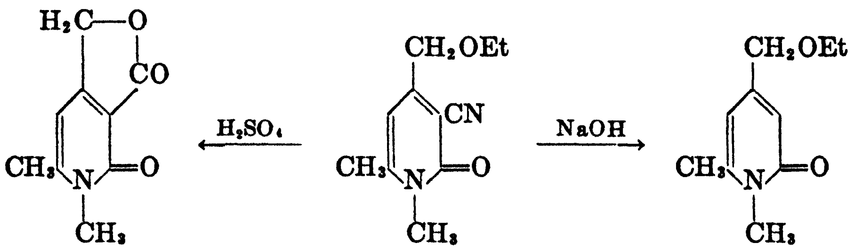


VII IX

An examination of the methylation reaction depicted in Equation B and the condensation reaction depicted in Equation C will show that of all the products only the one with structure VII can be formed in both reactions. A product was found which was common to both reactions and this obviously must possess structure VII. However, because the product VII obtained from the condensation reaction according to Equation C was difficult to purify and hence also difficult to identify positively by a mixed melting point determination, it was converted into the lactone X by refluxing with sulfuric acid. The identical lactone was also obtained from the product VII obtained from the methylation reaction according to Equation B. These findings leave no doubt about the structure of compound VII. It must be 1,6-dimethyl-3-cyano-4-ethoxymethyl-2-pyridone.

Having thus identified the compound VII, the next step was to convert it into compound IV. This conversion was readily accomplished by heating with dilute alkali at 170°, a procedure already described by us (4, 5). The resulting product is neutral but forms a well-crystallized picrate.

EQUATION D



X VII IV

The same compound IV, identified through its picrate, was obtained as a result of the decarboxylation of one of the products from the reaction of chloroacetic acid with 4-ethoxymethyl-6-methyl-2-pyridone (I). This product must thus have the N-acetic acid structure II.

Having thereby established the structure of one of the compounds definitely as the N-acetic acid, there remains no doubt that the isomeric compound found in the reaction must be the O-acetic acid.

Acknowledgment. Our thanks are due to Dr. A. Steyermark for microanalyses and to Mr. A. Motchane for absorption spectra.

EXPERIMENTAL

Part I. Reaction of 4-ethoxymethyl-6-methyl-2-pyridone with chloroacetic acid

A mixture of 235 g. of 4-ethoxymethyl-6-methyl-2-pyridone (4, 5) and 450 cc. of water was surrounded with a bath at 94° and treated at 5-minute intervals with 20 cc. of sodium hydroxide solution and 20 cc. of chloroacetic acid solution in water. The total volume of each solution used was 700 cc. containing respectively 226 g. of sodium hydroxide and 400 g. of chloroacetic acid. At the conclusion of the addition (about 3 hours) the mixture was stirred for an additional hour at 94° and then cooled in an ice-bath. Powdered sodium bicarbonate was added to bring the *p*H to about 7, and the whole was extracted 4 times with 300 cc. of chloroform to remove starting material. To the aqueous layer was added 450 cc. of concentrated hydrochloric acid and the acid solution was distilled to dryness *in vacuo*.

The residue was digested with 400 cc. of hot chloroform and filtered hot. The insoluble precipitate was digested twice more with 200 cc. of hot chloroform. The combined chloroform liquors from the digestion were distilled to dryness *in vacuo*, the residue was dissolved in 1100 cc. of methanol, and 160 g. of hydrogen chloride was passed into the mixture with cooling in an ice-bath. The mixture was refluxed for 8 hours and allowed to stand 3 weeks, when again the solvent was removed *in vacuo* below 60°.

To the residue, now containing the methyl esters, was added 100 g. cracked ice, and with further cooling in an ice-bath 50% (by weight) potassium carbonate solution to bring the *p*H to 7.5–8.0. The mixture was extracted 4 times with 300 cc. of ether and the ether extracts were dried with sodium sulfate, and distilled. A fraction, weighing 26.6 g. was obtained at 125–140° at 0.3 mm., and another fraction, weighing 21.2 g. at 170–175° at 0.3 mm.

A. 4-Ethoxymethyl-6-methyl-2-pyridyloxyacetic acid (III). The fraction boiling at 125–140°/0.3 mm. and 100 cc. of concentrated hydrochloric acid were heated on the steam-bath for 2 hours in an evaporating dish of 500 cc. capacity. After standing for some time crystals formed. These were filtered through a sintered glass funnel and dried in a desiccator over potassium hydroxide. The crystals weighed 20.3 g. and melted at 109–112°. They can be crystallized from alcohol-ether, acetone, or dilute hydrochloric acid. The purified product melted at 114–117°. The product was dried over P_2O_5 at room temperature at the oil-pump. The analysis indicates that the product is the hydrochloride of 4-ethoxymethyl-6-methyl-2-pyridyloxyacetic acid.

Anal. Calc'd for $C_{11}H_{15}NO_4 \cdot HCl$: C, 50.47; H, 6.16; N, 5.35.
Found: C, 49.36; H, 6.30; N, 5.63.

Drying at a higher temperature gave analyses which indicated that hydrogen chloride was being driven off. On the other hand drying in a vacuum desiccator over potassium hydroxide, previously evacuated at the water-pump, gave a product whose neutral equivalent indicated it contained a molecule of water.

Anal. Calc'd for $C_{11}H_{15}NO_4 \cdot HCl \cdot H_2O$: Neut. equiv., 140. Found: Neut. equiv., 138.

Thus, it is seen that incomplete drying leads to a low carbon analysis due to incomplete removal of water. To ensure a satisfactory analysis the benzylthiuronium salt was then prepared by adding 0.36 g. benzylthiuronium chloride to a solution of 0.50 g. of the hydrochloride and 3.6 cc. of *N* sodium hydroxide. The compound melted at 146–147° after crystallization from acetone.

Anal. Calc'd for $C_{19}H_{25}N_3O_4S$: C, 58.29; H, 6.44.
Found: C, 58.47; H, 6.43.

B. 4-Ethoxymethyl-6-methyl-2-pyridone-N-acetic acid. The fraction boiling at 170–175°/0.3 mm. and 100 cc. of concentrated hydrochloric acid were heated on the steam-bath for 2.5 hours in an evaporating dish of 500 cc. capacity. After adding 40 cc. of water, the mixture was scratched to induce crystallization. On drying the crystals weighed 12 g. and melted at 90–95°. These crystals represented a mixture of 4-ethoxymethyl-6-methyl-2-pyridone-N-acetic acid and its hydrochloride. Crystallization from water yielded 7.6 g. of the free N-acetic acid. Recrystallization from acetone or water gave the pure product, melting at 143–144°.

Anal. Calc'd for $C_{11}H_{15}NO_4$: C, 58.65; H, 6.71.
Found: C, 58.93; H, 6.73.

Part II. Methylation of 3-cyano-4-ethoxymethyl-6-methyl-2-pyridone (VI)

A. 2-Methoxy-3-cyano-4-ethoxymethyl-6-methylpyridine (VIII). A mixture of 460 g. of 3-cyano-4-ethoxymethyl-6-methyl-2-pyridone, 900 cc. of water, and 720 cc. of 16.7% (by weight) sodium hydroxide in water was warmed and stirred on the steam-bath, while 285 cc. of dimethyl sulfate was added during about an hour. The mixture was warmed and stirred for about 30 minutes longer, when an additional 60 cc. of dimethyl sulfate was added during 20 minutes. After 15 minutes this was followed by 120 cc. of 16.7% alkali. The treatment with 60 cc. of dimethyl sulfate and 120 cc. of alkali was repeated three times more. At the conclusion, 30 cc. of additional alkali was added, and the mixture was cooled to 5° and kept there for 17 hours. The resulting crystals were filtered and while still moist they were re-

crystallized from one liter of 50% methanol and again from 300 cc. of methanol. Thus a somewhat impure 2-methoxy-3-cyano-4-ethoxymethyl-6-methylpyridine was obtained. A further amount could be obtained by adding 200 cc. of water to the methanol filtrate and allowing the mixture to crystallize. The product was purified by crystallization from methanol containing a few drops of water. In this manner 23.5 g. of pure 2-methoxy-3-cyano-4-ethoxymethyl-6-methylpyridine, m.p. 80–81° was obtained.

Anal. Calc'd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.59.
Found: C, 64.36; H, 6.68; N, 13.30.

B. 1,6-Dimethyl-3-cyano-4-ethoxymethyl-2-pyridone (VII). All the methanolic filtrates from A were combined and distilled to dryness *in vacuo*. The residue was extracted repeatedly by stirring a few minutes with 500-cc. portions of boiling water and decanting. An almost pure 1,6-dimethyl-3-cyano-4-ethoxymethyl-2-pyridone (VII) was obtained in the form of plates when the aqueous extracts were allowed to cool slowly with occasional stirring. The pure product melts also at 80–81°, after crystallization from carbon tetrachloride. It gave a depression in melting point, when mixed with 2-methoxy-3-cyano-4-ethoxymethyl-6-methylpyridine from Part IIA; yield 196 g.

Anal. Calc'd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84.
Found: C, 63.82; H, 6.65.

C. Lactone of 1,6-dimethyl-3-carboxy-4-hydroxymethyl-2-pyridone (X). A mixture of 5.5 g. of the product from Part B above and 28 cc. of 50% (by weight) sulfuric acid was refluxed for 3 hours and then poured into 75 cc. of water. In this manner 4.3 g. of almost pure lactone was obtained. The pure product, obtained by crystallization from water, melts at about 270° with decomposition. The melting point varies with the rate of heating.

Anal. Calc'd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82.
Found: C, 60.18; H, 5.27; N, 7.67.

Part III. Reaction of cyanoacetmethylamide with ethoxyacetylacetone

A. Isolation of 1,6-dimethyl-3-cyano-4-ethoxymethyl-2-pyridone (VII). A solution of 9.8 g. of cyanoacetmethylamide, 14.4 g. of ethoxyacetylacetone, one cc. of piperidine and 70 cc. of ethanol was refluxed during 2 hours and 45 minutes. The ethanol was removed on the steam-bath and the residue was triturated with petroleum ether. In this manner 20.5 g. of solid product was obtained. When 5 g. of this product was crystallized twice from water only 0.85 g. of impure crystals, m.p. 68–78° was obtained. These crystals were recrystallized from carbon tetrachloride to give a product melting at 73–77°. A mixed melting point with the product from Part II B showed no depression. Further crystallization from carbon tetrachloride did not raise the melting point. In line with the argument presented in the theoretical part of this paper, this product must also be 1,6-dimethyl-3-cyano 4-ethoxymethyl-2-pyridone (VII). Further proof is presented below.

B. Conversion to lactone of 1,6-dimethyl-3-carboxy-4-hydroxymethyl-2-pyridone (X). In an experiment carried out as described in Part III A, the residue remaining after trituration with petroleum ether was refluxed with 100 cc. of 50% (by weight) sulfuric acid for one hour and 20 minutes. The mixture was poured into 200 cc. of H_2O and allowed to crystallize. In this manner 5.38 g. of almost pure lactone was obtained. After crystallization from water it melted at 270° with decomposition. The ultraviolet absorption spectrum is identical with that of the product from Part II C with maxima at 236 and 325 mμ and minima at 230 and 264 mμ.

Anal. Calc'd for $C_9H_9NO_3$: C, 60.33; H, 5.06.
Found: C, 60.36; H, 5.38.

C. Isolation of 1,4-dimethyl-3-cyano-6-ethoxymethyl-2-pyridone (IX). The sulfuric acid filtrate after crystallization of the lactone X in Part III B was extracted twice with 100 cc. of chloroform and the chloroform was distilled off. The residue was dissolved in hot water and to the hot solution was added 20 cc. of 10% sodium hydroxide. On cooling 2 g. of 1,4-dimethyl-3-cyano-6-ethoxymethyl-2-pyridone was obtained. After crystallization from water it melted at 127–128°.

Anal. Calc'd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.86; N, 13.59.
Found: C, 63.60; H, 6.66; N, 13.12.

Part IV. 1,6-Dimethyl-4-ethoxymethyl-2-pyridone (IV)

A mixture of 20 g. of 1,6-dimethyl-3-cyano-4-ethoxymethyl-2-pyridone (VII), obtained from Part II B, 94 cc. of 10% sodium hydroxide and 106 cc. of water was heated in an autoclave at 170° for 24 hours with occasional shaking. After cooling it was extracted four times with 50 cc. of chloroform. The chloroform extracts were dried with sodium sulfate and distilled. At 130–135° and 0.2 mm., 13.4 g. of 1,6-dimethyl-4-ethoxymethyl-2-pyridone distilled over; d_{25}^{25} 1.084; n_D^{27} 1.5379.

To a solution of one gram of this material in ether was added a saturated solution of picric acid in ether until no further precipitate was obtained. In this manner 2.04 g. of almost pure picrate was obtained. After crystallization from about 8 cc. of ethanol, it weighed 1.71 g. and melted at 108–110°.

Anal. Calc'd for $C_{16}H_{18}N_4O_9$: C, 46.83; H, 4.42.
Found: C, 46.85; H, 4.54.

Part V. Decarboxylation of 4-ethoxymethyl-6-methyl-2-pyridone-N-acetic acid (II)

One pellet of sodium hydroxide was powdered and added to 0.50 g. of 4-ethoxymethyl-6-methyl-2-pyridone-N-acetic acid, m.p. 143–144°, from Part I. The mixture was heated in an air-bath at 210–230° under a pressure of 0.2 mm. in a short distilling flask until no further distillate was obtained. The distillate was dissolved in ether and treated with a saturated solution of picric acid in ether. On standing 0.16 g. of picrate, m.p. 102–107° was obtained. After recrystallization from ethyl alcohol it melted at 106–108°. It gave no depression in melting point when mixed with the picrate of 1,6-dimethyl-4-ethoxymethyl-2-pyridone from Part IV. The ultraviolet absorption spectra were identical with maxima at 314 and 365 mμ and minima at 273 and 328 mμ.

Anal. Calc'd for $C_{16}H_{18}N_4O_9$: C, 46.83; H, 4.42.
Found: C, 47.10; H, 4.38.

NUTLEY 10, N. J.

SUMMARY

The reaction of a pyridone with chloroacetic acid has been found in one particular instance to yield besides the N-acetic acid derivative an O-acetic acid derivative. The structure of the former was established by unambiguous methods.

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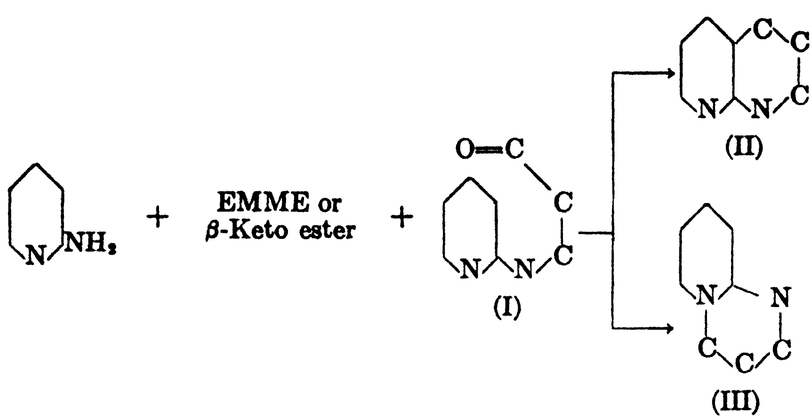
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF DUKE UNIVERSITY]

CYCLIZATION OF 2-AMINOPYRIDINE DERIVATIVES TO FORM 1,8-NAPHTHYRIDINES

CHARLES R. HAUSER AND MARTIN J. WEISS[1]

Received December 27, 1948

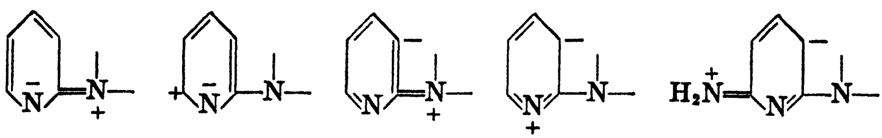
The EMME, Conrad-Limpach, and Knorr methods have been particularly successful for the synthesis of certain 2- or 4-hydroxyquinolines (1). The reactions involve the condensation of an aniline with EMME (ethoxymethylenemalonic ester) or a β-keto ester, and the cyclization of the resulting anil, crotonate, or anilide. The adaptation of these reactions to the synthesis of the corresponding 1,8-naphthyridines (II) by employing 2-aminopyridines instead of anilines should furnish convenient methods for the preparation of these types of compounds since 2-aminopyridines are readily available. However, these methods have not been as satisfactory for the preparation of 1,8-naphthyridines as for the preparation of quinolines. In contrast to anilino derivatives, 2-aminopyridine derivatives (I) may cyclize in two ways, one leading to the formation of 1,8-naphthyridines (II) and the other to the formation of pyrimidines (III). Actually the latter course of reaction often occurs. The two courses of reaction may be indicated schematically as follows:



In both types of cyclization, the pyridine ring functions as the electron donor and the carbonyl group in the side chain serves as the electron acceptor. The mechanism is presumably analogous to that of other electrophilic substitutions into aromatic rings such as the Friedel-Crafts type of reaction. The formation of pyrimidines is not surprising since resonance structure (IV), which may be considered an activated form leading to pyrimidines, probably contributes considerably to the structure of the 2-aminopyridine derivative (I). There is evidence (2) that this resonance structure makes the main contribution to the structure of 2-aminopyridine itself. The electron donating capacity of the

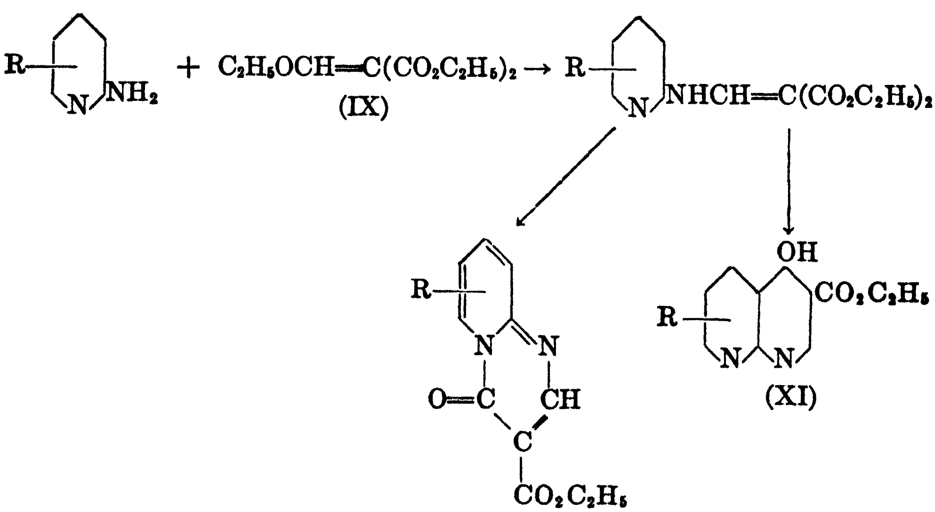
[1] Eli Lilly Fellow, 1947–1948.

heterocyclic nitrogen may be further enhanced by contributions of the resonance structures such as (V) which have been considered characteristic of the pyridine ring (3). Resonance structures (VI) or (VII) (4), which may be considered activated forms leading to 1,8-naphthyridines, might also make important contributions but usually further activation at the 3-position or deactivation at the heterocyclic nitrogen appears to be required for this cyclization to be realized. Thus, although the formation of the pyrimidine often occurs, the naphthyridine is formed with the 6-amino derivative in which resonance structure (VIII) may make an important contribution to the structure of the molecule. The 6-amino group might also activate the heterocyclic nitrogen but, in this instance, cyclization at this position appears to be hindered sterically (5).



(IV) (V) (VI) (VII) (VIII)

In agreement with these considerations, Lappin (5) has shown that, in the reaction with EMME (IX), the pyrimidine (X) is normally formed. However, the corresponding 1,8-naphthyridines (XI) are produced when R is 6-amino (6), 6-ethoxy (5) or 6-methyl (5).

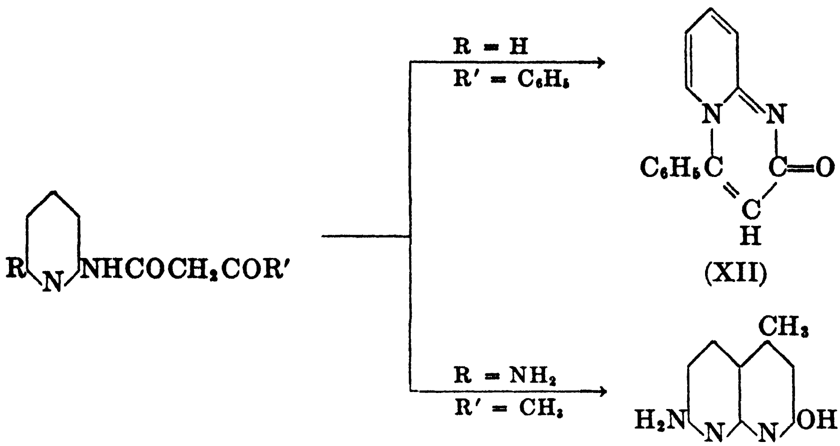


(IX) (XI)

(X)

Similarly, the amide from 2-aminopyridine and ethyl benzoylacetate cyclizes to form the pyrimidine (XII) (7). However the Knorr type of reaction to form a 1,8-naphthyridine (XIII) has been realized with the amide of 2,6-diaminopyridine and ethyl acetoacetate (8).

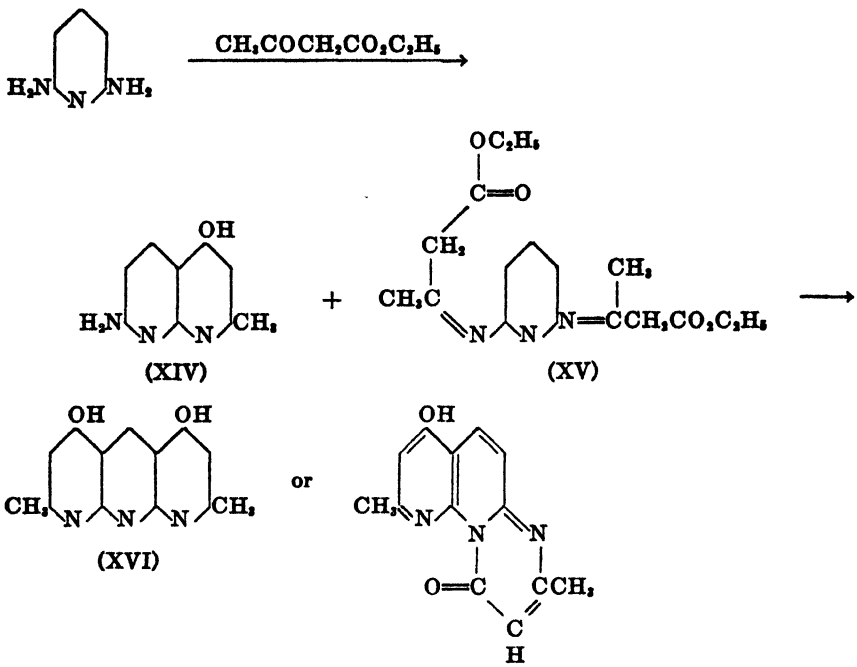
In the present investigation similar results have been obtained in the Conrad-Limpach reaction, which involves the cyclization of an anil or a crotonate formed from the condensation of a β-keto ester with an aromatic amine. With 2-amino-



pyridine and ethyl acetoacetate, a product was obtained which appeared to be the pyrimidine although it did not analyze very satisfactorily. It had a relatively low melting point, was soluble in various organic solvents and was hydrolyzed by alkali to 2-aminopyridine. Lappin (5) has found that somewhat similar pyrimidines, obtained with EMME, also exhibited these characteristics. However, with 2,6-diaminopyridine and ethyl acetoacetate, the Conrad-Limpach type of cyclization was evidently realized. Rather surprisingly, this cyclization to form the naphthyridine (XIV) appeared to occur at room temperature under the conditions generally employed for the preparation of the anil or crotonate, except that the time of reaction was considerably longer. That the product is a naphthyridine rather than a pyrimidine, was indicated by its high melting point and its insolubility in most organic solvents. Lappin (5) has shown that the naphthyridines obtained from EMME exhibit similar properties.

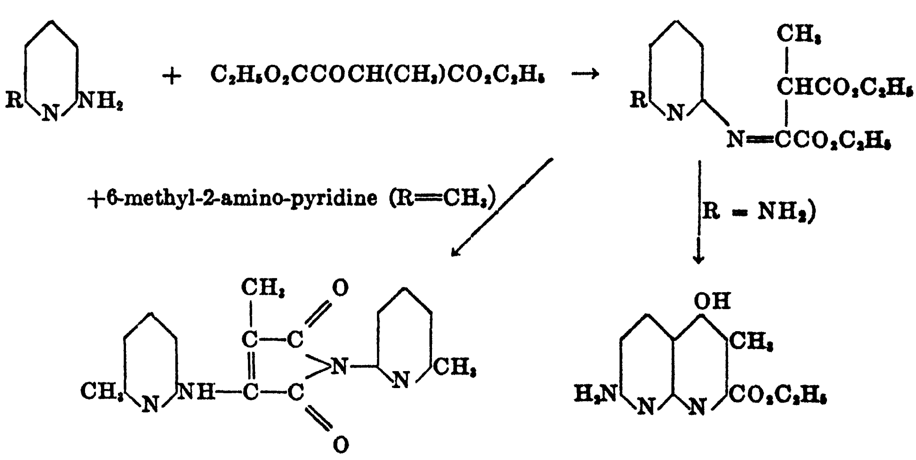
In addition to the naphthyridine (XIV), there was obtained a product which was evidently the dianil (XV). This substance was readily separated from the naphthyridine by extraction of the mixture with hot ligroin in which the dianil was soluble. That this substance is the dianil (XV) was shown not only by its analysis but also by its cyclization to a product which analyzed either for a pyridonaphthyridine (XVI) or a pyrimidonaphthyridine (XVII). The cyclized product gave a positive enol test with ferric chloride.

Similarly with 2,6-diaminopyridine and ethyl α-ethoxalylpropionate, which may be regarded as a β-keto ester, the Conrad-Limpach reaction appeared to occur to form (XIX), although the pure product has not been isolated. In this case also, the cyclized product was obtained under conditions which generally give only the anil (refluxing in ethanol over Drierite) (9). That the product was the naphthyridine (XIX) was indicated by its high melting point and by its solubility in sodium hydroxide solution but not in sodium bicarbonate solution. With 2-aminopyridine or 6-methyl-2-aminopyridine and ethyl α-ethoxalylpropionate, neither a naphthyridine nor a pyrimidine appeared to be formed. A pure product was isolated with the 6-methyl derivative but this was evidently



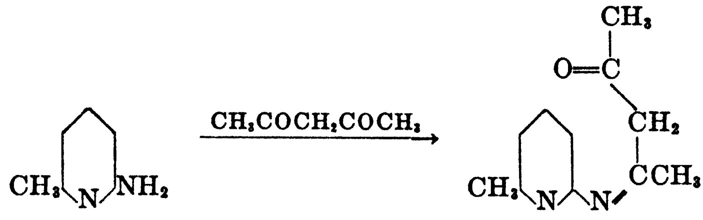
(XIV) (XV) (XVI) (XVII)

the maleimide (XVIII), which could have resulted from the reaction of the anil with a second molecule of 6-methyl-2-aminopyridine. The formation of a similar maleimide has been reported by Surrey and Cutler (10) from the reaction of *m*-chloroaniline with the anil from this amine and ethyl α-ethoxalylpropionate. It seems likely that the yield of maleimide (XVIII), could be improved by using two molecular equivalents of the 2-aminopyridine instead of the one equivalent employed in this investigation.



(XVIII) (XIX)

Although Mangini and Colonna (11) have reported the formation of 2,4-dimethyl-7-amino-1,8-naphthyridine from 2,6-diaminopyridine and acetylacetone, we have been unable to effect the analogous reaction of 6-methyl-2-aminopyridine and acetylacetone even after first isolating the corresponding anil (XX). It is of interest that an attempt to prepare the picrate of this anil led to hydrolysis of the compound, the picrate of 6-methyl-2-aminopyridine being obtained.



(XX)

EXPERIMENTAL[2]

Ethyl acetoacetate with 2-aminopyridine. To a solution of 9.4 g. (0.10 mole) of 2-aminopyridine in 13.0 g. (0.10 mole) of ethyl acetoacetate was added four drops of concentrated hydrochloric acid solution and the solution placed in an evacuated desiccator over concentrated sulfuric acid. After seven days, the solution was distilled through an 11 cm. Vigreux column yielding, after a forerun of starting materials, 7.4 g. of product boiling at approximately 143° at 3.5 mm., the product solidifying on cooling. After one recrystallization from benzene-Skellysolve B, the product (white crystals) melted at 115–117°, and, after four additional recrystallizations it melted at 120–120.5° with some shrinking at 80°. This substance was apparently 4-methyl-2*H*-pyrido[1,2-*a*]pyrimidin-2-one.

Anal.[3] Calc'd for $C_9H_8N_2O$: C, 67.49; H, 5.04; N, 17.49.
Found: C, 66.88; H, 5.14; N, 17.02.

This substance was soluble in benzene, ethanol, methanol, acetone, and water. It was recovered unchanged after refluxing in 10% hydrochloric acid solution for two hours, but it was hydrolyzed by hot 10% sodium hydroxide solution to form *2-aminopyridine*, m.p. 48–53°; reported m.p. 56° (12). The *picrate* melted at 222–223°; reported m.p. 217° (13). A mixed melting point with an authentic sample of the picrate (m.p. 221–222°) showed no depression.

Ethyl acetoacetate with 2,6-diaminopyridine. To a partial solution of 25.0 g. (0.217 mole) of 2,6-diaminopyridine in 28.2 g. (0.217 mole) of ethyl acetoacetate was added eight drops of concentrated hydrochloric acid solution and the mixture was kept in an evacuated desiccator over concentrated sulfuric acid for thirty-three days. The product was thoroughly washed with water, dried in air, and refluxed with 100 ml. of ligroin (b.p. 70–90°). The suspension was filtered and the solid washed once with ligroin. The solid (3.0 g., 8%) was 2-methyl-4-hydroxy-7-amino-1,8-naphthyridine (XIV), melting above 360°, which was insoluble in hot 10% sodium hydroxide solution, was unaffected by several hours boiling in a 6 *N* hydrochloric acid solution and was insoluble in ethanol, ispropyl ether, dioxane, butanol, ethyl acetate, pyridine, Methyl Cellosolve and chloroform. One recrystallization from quinoline yielded a white powder, m.p. > 360°, which was thoroughly washed with acetone and ether.

Anal.[5] Calc'd for $C_9H_9N_3O$: C, 61.71; H, 5.18; N, 23.99.
Found: C, 61.63, 61.59; H, 5.02, 4.91; N, 23.86.

[2] Boiling points and melting points are uncorrected.
[3] Analysis by Clark Microanalytical Laboratory, Urbana, Illinois.
[4] Analysis by the University of Pittsburgh Microchemical Laboratory.
[5] Analysis by Oakwold Laboratories, Alexandria, Virginia.

The solvent was evaporated from the filtrate obtained from the treatment of the reaction mixture with ligroin, leaving 6.6 g. (13%) of crude *dianil* (XV), m.p. 61–67°. Several recrystallizations from ligroin (b.p. 70–90° gave crystals of (XV) melting at 76°.

Anal.[3,4] Calc'd for $C_{17}H_{23}N_3O_4$: C, 61.24; H, 6.95; N, 12.60.
Found: C, 61.16, 61.47; H, 6.82, 6.66; N, 12.75.

The crude *dianil* (1.0 g., m.p. 61–67°) was dissolved in 5 ml. of warm Dowtherm A and the solution was refluxed for ten minutes. After cooling, 25 ml. of ligroin was added. The brown solid was filtered off and washed with ligroin yielding 0.6 g. of material which was extracted with ether in a Soxhlet extractor. Evaporation of the solvent from the ether extracts yielded 0.45 g. of a product, melting at 210–220° dec., which, after several recrystallizations from ethanol-water and from ethanol-isopropyl ether, gave white crystals melting at 230–231°. This substance analyzed either for compound (XVI) or compound (XVII), both of which have the same empirical formula.

Anal.[3, 4] Calc'd for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.60; N, 17.42.
Found: C, 64.36; H, 4.91; N, 17.42, 17.43.

Ethyl α-ethoxalylpropionate with 6-methyl-2-aminopyridine. A solution of 21.2 g. (0.10 mole) of ethyl α-ethoxalylpropionate, 10.8 g. (0.10 mole) of 6-methyl-2-aminopyridine and six drops of glacial acetic acid in 50 ml. of commercial absolute ethanol was refluxed on the steam-bath for 18 hours with 30 g. of Drierite. The hot mixture was filtered and most of the solvent was removed with a water aspirator. The residue, which partly solidified on standing overnight, appeared to contain some of the maleimide (XVIII) but attempts to isolate the product at this stage were unsuccessful. A solution of the residue in xylene was refluxed for thirty minutes. The solution was poured into a large excess of Skellysolve B. The oil which separated became, after several hours, a waxy semi-solid from which was decanted the xylene-Skellysolve B solution. An ethanol solution of the semi-solid was treated with Norit and, after evaporating the solution to approximately 40 ml., an equal volume of water was added. After chilling, the yellow crystals were filtered off and recrystallized from ethanol-water yielding 1.6 g. (10%) of *α-(6-methyl-2-pyridoamino)-N-(6-methyl-2-pyridyl)-β-methylmaleimide* (XVIII), melting at 195–197°. Several additional recrystallizations from ethanol-water gave yellow crystals melting at 198.5–200°.

Anal.[3] Calc'd for $C_{17}H_{16}N_4O_2$: C, 66.22; H, 5.22; N, 18.17.
Found: C, 66.02, 65.89; H, 5.34, 5.35; N, 18.20, 18.12.

Ethyl α-ethoxalylpropionate with 2,6-diaminopyridine. To a solution of 10.6 g. (0.05 mole) of ethyl α-ethoxalylpropionate and 5.8 g. (0.05 mole) of 2,6-diaminopyridine in 50 ml. of commercial absolute ethanol was added three drops of glacial acetic acid and 15 g. of Drierite. The mixture was refluxed twelve hours, then filtered. The filtrate was poured into 400 ml. of water yielding 5.0 g. (40%) of a yellow-brown solid, melting at about 300–305° dec., which was apparently *2-carbethoxy-3-methyl-4-hydroxy-7-amino-1,8-naphthyridine* (XIX). Several recrystallizations from ethanol-water did not produce a pure substance. The product readily dissolved in 10% sodium hydroxide solution and was reprecipitated by carbon dioxide. On refluxing in a 10% sodium hydroxide solution, followed by acidification, an acid was obtained; however, the pure acid was not isolated.

Acetylacetone with 6-methyl-2-aminopyridine. A solution of 9.4 g. (0.10 mole) of 6-methyl-2-aminopyridine and 10.0 g. (0.10 mole) of acetylacetone was refluxed for five hours and then distilled through an 11 cm. Vigreux column yielding, after a forerun of starting material, 5.8 g. (31%) of *anil* (XX) boiling at 138–139° at 5 mm. On redistillation and after several recrystallizations of the resulting solid from Skellysolve B, white crystals were obtained melting at 74.5–75.5°.

Anal.[3] Calc'd for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.73.
Found: C, 69.06; H, 7.26; N, 14.34.

In an attempt to prepare the picrate of the anil in ethanol in the usual manner, the *picrate* of *6-methyl-2-aminopyridine* was obtained instead. The picrate of the amine melted

at 202–203° [reported m.p. 202° (14)]. A mixed melting point with an authentic sample (m.p. 202–204°) showed no depression.

SUMMARY

Certain of the theoretical aspects of some of the synthetic methods used for the preparation of 1,8-naphthyridines from 2-aminopyridine derivatives have been considered.

An investigation of the synthesis of certain 1,8-naphthyridines from 2-aminopyridines with ethyl acetoacetate or ethyl α-ethoxalylpropionate by the Conrad-Limpach reaction has been made.

DURHAM, NORTH CAROLINA

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[Contribution from Mellon Institute and the Chemistry Department, University of Pittsburgh]

A STUDY OF THE POLYMERIZATION PRODUCTS OF DIKETENE[1,2]

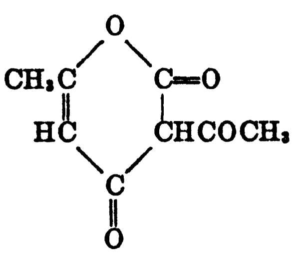
ARTHUR B. STEELE, ALBERT B. BOESE, and MALCOLM F. DULL

Received December 27, 1948

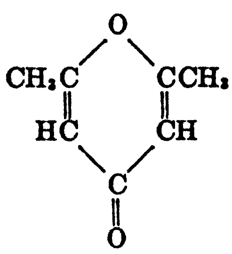
INTRODUCTION

Although a considerable amount of literature on the polymerization of diketene has developed in recent years (1–5), there appears to have been no study of the mechanism of the polymerization nor of the chemical nature of the products other than the ketene tetramer, dehydracetic acid. This study was undertaken with the object of discovering the course of the reaction, and more particularly of characterizing any additional polymerization products which might be isolated.

Although pure diketene is relatively stable, and not subject to polymerization alone or in neutral solvents at temperatures below 0°, it does undergo ready polymerization at elevated temperatures and in the presence of other materials such as acids, alkalis, and certain salts. With complete transformation of the monomer there is obtained a viscous to semi-solid mass of deep red color. We have now resolved this mixture into three pure components, the expected dehydracetic acid (I) and two others that have not been reported by other investigators.



(I)



(II)

Diketene of 99.5% purity was polymerized in boiling benzene solution in the presence of sodium phenoxide, according to the procedure of Boese (5). Carbon dioxide was evolved. Processing the reaction products led to the isolation of (I) in 54% yield, 2,6-dimethylpyrone (II) in 4% yield, and a white solid (III), $C_{19}H_{16}O_6$, in 8% yield.

The same products were obtained on polymerization of diketene in benzene, toluene, and xylene solution in the presence of either sodium phenoxide, sodium acetate, tributyl-, or triethyl-amine. Treatment of pure dehydracetic acid under the same conditions caused no reaction.

The chemical nature of (III) is indicated by a variety of means, including infrared and ultraviolet absorption studies and chemical tests. It is a neutral

[1] Presented before the Division of Organic Chemistry, 113th Meeting, American Chemical Society, Chicago, Illinois, April 19–23, 1948.

[2] Abstracted from a thesis submitted by Arthur B. Steele in partial fulfillment of the requirements for the degree of doctor of philosophy.

substance containing no reactive functional groups, characterized by pronounced susceptibility to oxidation, hydrogenolysis, and absorption of bromine from the liquid state.

Examination of the ultraviolet absorption curve (Fig. 1) in the light of the findings of other investigators (6–10) leads to a number of conclusions regarding the substance.

1. No benzenoid system is present.
2. The maximum at $\lambda = 3020$ Å indicates the presence of at least one pair of closely associated double bonds, one of which may be a carbonyl bond, although the ketone band at 2800 Å is absent. An enolic structure is not indicated.

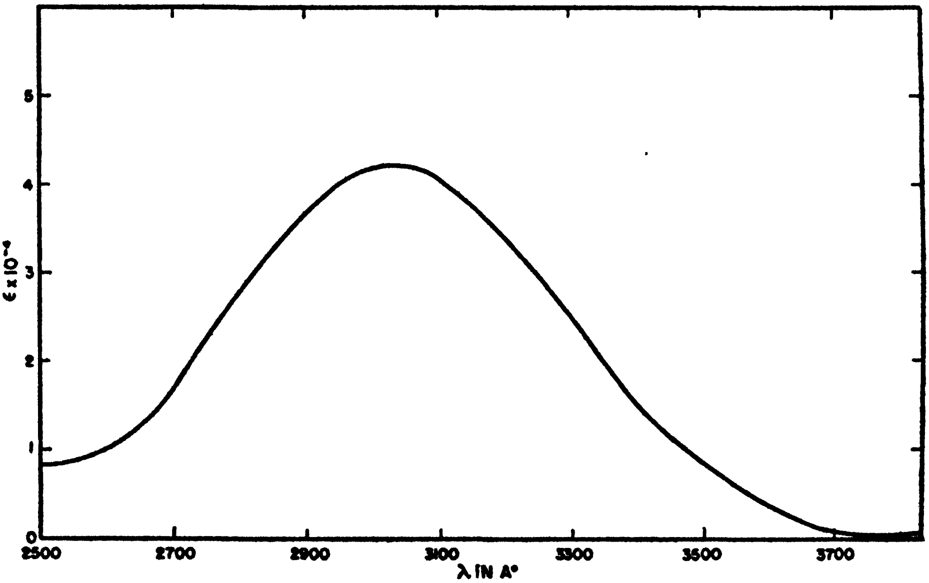


FIG. 1. SPECTROSCOPIC STUDY. ULTRAVIOLET ABSORPTION SPECTRA
Unknown, 2.94 × 10^{-5} M. in acetic acid in 1 cm. cell.

3. The breadth of this parabolic band suggests the presence of several groups contributing as vectors to the maximum at 3020 Å.
4. There is marked similarity between this curve and those of diketene and dehydracetic acid.
5. The ϵ values of the substance and those of dehydracetic acid are of the same magnitude.

The infrared absorption data (Fig. 2) support the following conclusions (11):

1. Because absorption bands at wave lengths in excess of 10 microns are attributable to the vibrations of the molecule as a unit, these bands serve to "finger print" the molecule rather than to indicate presence or absence of functional linkages within the molecule.
2. The absence of "free" hydroxyl groups (in which the hydrogen atom is not affected by any atom except the oxygen to which it is bonded) is indicated, since no absorption is found between 3700 and 3500 cm.$^{-1}$.

3. Hydroxyl groups subject to intermolecular association and/or internal chelation might provide the band at 3330 cm.$^{-1}$.

4. The triple-bond structure appears to be absent, for no band is observed in the range of 2000–2300 cm.$^{-1}$.

5. The non-appearance of a double band at 1800–1850 cm.$^{-1}$ and 1750–1800 cm.$^{-1}$ indicates the absence of an anhydride group.

6. The absence of an ester carbonyl group is indicated by the lack of a band at 1725–1750 cm.$^{-1}$.

7. The very strong absorption at 1710 cm.$^{-1}$ suggests the presence of the keto carbonyl group.

8. The carboxyl structure appears to be absent, for no double band at 1660–1685 cm.$^{-1}$ and 3500–3700 cm.$^{-1}$ is evident.

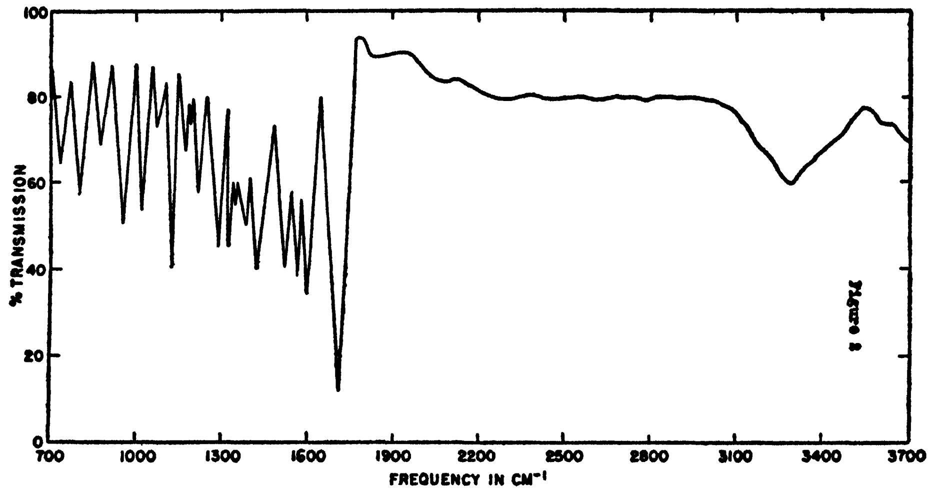


FIG. 2. SPECTROSCOPIC STUDY. INFRARED ABSORPTION

36% by weight of unknown in mineral oil paste. Rock salt disks, 11 microns apart.

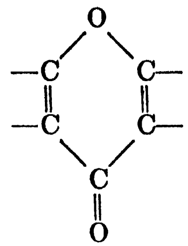
9. The absence of random aliphatic C═C linkages is indicated by the absence of a band at 1640–1660 cm.$^{-1}$. However, the presence of a conjugated aliphatic linkage is suggested by a band at 1600 cm.$^{-1}$. The carbon-carbon unsaturation of a benzenoid structure, giving rise to two bands at 1600 cm.$^{-1}$ and at 1500 cm.$^{-1}$, is not evidenced.

10. The bands at 1350, 1392, and 1410 cm.$^{-1}$ suggest the presence of methyl groups.

11. The triplet absorption band at 1350, 1392, and 1410 cm.$^{-1}$ indicates the presence of the γ-pyrone structure (12).

12. The ketene structure appears to be absent, for no band at 2150 cm.$^{-1}$ is evident.

The general conclusion to be drawn from ultraviolet and infrared absorption measurements is that (III) probably contains one or more γ-pyrone rings (IV) with methyl or substituted methyl side chains. This inference is supported by

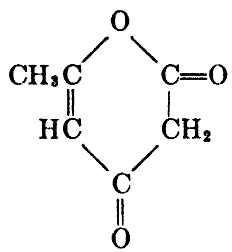


(IV)

an examination of the chemical properties of the substance. Chemical characterization, however, was complicated by the extreme insolubility of the substance in the usual solvents.

The absence of reactive functional groups is indicated by the negative results of all the usual qualitative tests except oxidation, hydrogenolysis, and bromination. Simple hydrogenation does not occur. An acetic acid solution of (III) was not affected by hydrogen at 1800 p.s.i. and 70° in the presence of platinum catalyst.

Clemmensen reduction gives triacetic lactone (V) and (II). It is believed



(V)

that (II) results from spontaneous dehydration of a precursor which is *sym*-diacetylacetone. Hydrogenolysis in the presence of various catalysts gives (I), (II), and (V), while reduction with hydrogen iodide yields (II).

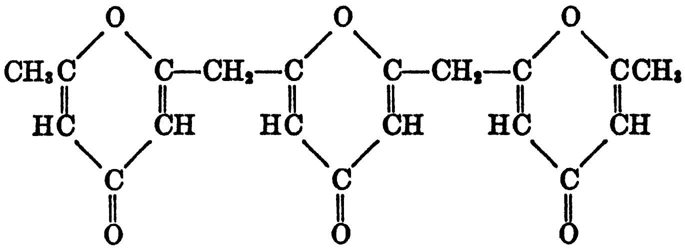
Oxidation with peracetic acid gives (V). Treatment with nitric acid at 40–45° gives four moles of oxalic acid per mole reacted. Oxidation with aqueous periodic acid gives oxalic and acetic acids and carbon dioxide, while treatment with lead tetraacetate in glacial acetic acid causes an evolution of carbon dioxide and the formation of tars. Kühn-Roth oxidation gives unreproducible results, but indicates that the molecule contains two or four carbons oxidizable to acetic acid.

Prolonged digestion with hydrochloric acid gives (V), while treatment with alkali results in complete disruption of the molecule.

Reaction with liquid bromine gives an unstable addition product which rapidly loses hydrogen bromide, giving $C_{19}H_{10}Br_6O_6$. This demonstrates the presence of six equivalent carbon-carbon double bonds with at least six hydrogen atoms in probably equivalent positions.

These observations accord with the view that the parent ring system is that of γ-pyrone (13).

Hydrogenolysis to (I), (II), and (V) under a variety of conditions, catalytic and otherwise, and resistance to simple hydrogenation are also indicative of pyrone rings, while the evidence of oxidation and of bromination is consistent with this view. Quantitatively, the presence of three pyrone rings is indicated by bromination. On the basis of the foregoing evidence, it is believed that (III) is 2,6-bis-(6-methyl-4-oxo-2-pyranylmethyl)pyrone.



This structure is believed to accord with the experimental facts which have been established, and it remains to consider the mechanism by which such a compound could be produced from diketene. The following molecular equation represents the over-all process.

$$5C_4H_4O_2 \rightarrow C_{19}H_{16}O_6 + CO_2 + 2H_2O$$

Carbon dioxide is evolved during the polymerization, while the formation of small amounts of acetone can be accounted for by the reaction of some diketene with water, giving acetoacetic acid which decomposes to acetone and carbon dioxide.

The basic catalyst may be considered to promote reaction of diketene as acetylketene, $CH_3COCH{=}C{=}O$. Condensation starts with two molecules giving (A), and continues until a C_{20} chain is reached (B).

A $CH_3COCH_2COCH_2COCH{=}C{=}O$

B $CH_3CO(CH_2COCH_2CO)_4CH{=}C{=}O$

C $CH_3CO(CH_2COCH_2CO)_4CH_3$

At this stage water adds at the ketene position and decarboxylation occurs to form (C). Enolization of (C) and dehydration gives rise to (III). If water adds at (A) instead of (B), the product of decarboxylation would be *sym*-diacetylacetone. The latter is subject to spontaneous loss of water, yielding (II), which was found.

No compound possessing two γ-pyrone structures within the molecule is anticipated by this mechanism, for such a compound would require a fractional number of diketene units in the linear polymer.

Probably the polymerization of diketene occurs through the carbonyl group and may be followed by rearrangement of the resultant enolic structures to those shown in the equations. This mode of addition would be analogous to the aldol type reaction proposed by Boese (14) for the formation of α,β-unsaturated methyl ketones by reaction of diketene with aldehydes. While this reaction

occurs readily under uncatalyzed conditions, the related reaction with methyl ketones was found in this work to occur very slowly at elevated temperatures, and not at all with other ketones. This result is in line with the known inertness of ketone carbonyl groups relative to those of aldehydes.

EXPERIMENTAL

Diketene. The diketene used in these studies was the commercial product of the Carbide and Carbon Chemicals Corporation. Before each experiment it was redistilled to give a material boiling at 64–65° at 80 mm., and freezing at −6.9°. By analysis a purity in excess of 99 per cent by weight was indicated.

Polymerization of diketene. To 1000 ml. of refluxing benzene containing 1 g. of sodium phenoxide, 900 g. of diketene was added during two hours with constant stirring. The polymerization being exothermic, the diketene was added at such a rate as to maintain refluxing without the application of external heat. During the polymerization it was noted that carbon dioxide was evolved concurrently with the addition of diketene. Quantitatively, approximately 12 mole per cent, based on diketene, was found in the vent gas. After all the diketene had been introduced, refluxing was continued for one hour after which the resulting red solution was allowed to stand at room temperature for sixteen hours. At the end of this time, the odor of diketene had entirely disappeared.

The crude crystalline material which separated was filtered and washed with methanol, the washings being combined with the filtrate. A first crop of 489 g. of crude dehydracetic acid was thus obtained. By concentrating the filtrate to half its original volume on the steam-bath a second crop of 110 g. was recovered from the cooled mother liquor. Small quantities of acetone were detected in the distillate.

The crude acid was dissolved in 1500 ml. of hot methanol and filtered while hot. While most of the crude product was soluble there did remain 58 g. (8%) of a methanol-insoluble material which on recrystallization from glacial acetic acid appeared as a colorless crystalline substance melting at 235–236°.

From the cooled methanol filtrate there was obtained 491 g. (54%) of pure dehydracetic acid, identified by a mixed melting point determination with known material.

The benzene solution remaining from the separation of dehydracetic acid was freed of benzene by low-pressure stripping and the residue distilled under vacuum. A fraction of 41 g., boiling at 140–145° at 10 mm., was recovered. The residue, a dark tarry material, could not be further distilled.

The distillate was redistilled, giving 27 g. (4%) of product boiling at 136–138° at 14 mm. Recrystallization of this material from acetone gave pure 2,6-dimethylpyrone, melting at 131–132°, and identified by analysis, mixed melting point, and conversion to γ-lutidone (15). The still residue was recrystallized from methanol and found to be mainly dehydracetic acid.

IDENTIFICATION OF THE UNKNOWN SUBSTANCE

Solubility. The unknown substance (III) from the above separation is virtually insoluble in all common solvents except boiling 1,4-dioxane and glacial acetic acid, in which it dissolves to the extent of 7.2 grams and 5.2 grams, respectively, per 100 grams of solvent at the boiling point.

Analysis. Qualitative analysis showed the presence of only carbon and hydrogen. Combustion gave C, 67.10%; H, 4.75%; and O (by difference), 28.15%.

Molecular weight. The molecular weight was determined by the method of comparative ebulliometric measurement developed by Swietoslawski (16). Acetic acid was chosen as the best solvent for this purpose. Glacial acetic acid, the boiling temperature of which was 0.064° higher than the condensation temperature, was used in an improved simple

ebulliometer in series with a differential ebulliometer[3]. The data indicate a molecular weight of 339.

Ultraviolet absorption measurements. All determinations were made in glacial acetic acid, distilled until the distillate passed the ebulliometric specifications stated above.

The ultraviolet data were obtained photographically with a standard Beckman spectrophotometer, the light source being a hydrogen discharge tube between 2200 and 3200 Å and a tungsten filmament above 3200 Å. A built-in Brown recorder registered per cent transmission of light directly. The spectrum was examined from 2500 Å to 3800 Å at 10 Å intervals. The result is shown in Fig. 1.

Infrared absorption measurements[4]. A sample of (III) was finely ground and mixed with mineral oil to form a paste containing 36% by weight of the unknown. This paste was pressed between two rock-salt discs so that the optical path between the discs was about 11 microns long. The infrared absorption of this assembly was then compared to that of another similar assembly in which the material between the discs was mineral oil alone.

The comparison was made on a Perkin-Elmer infrared spectrometer provided with wavelength drive, automatic signal attenuator, a General Motors amplifier, and a Brown recorder. The resulting spectra were recorded on a photostatic reproduction. The percentage transmission, I/I_0, over the entire wave length from 1.2 to 16.2 microns was calculated. To provide a graphic representation of the data, a plot of percentage transmission and wave number as abscissa and ordinates, respectively, is shown in Fig. 2.

Bromination. A solution of 11 g. of (III) in 150 g. of liquid bromine was sealed in glass and stored at 2° to 4° for ten days. Excess bromine was removed by distillation, leaving a viscous red oil which, even at ordinary temperatures, spontaneously lost hydrogen bromide with the production of a yellow solid. On recrystallization from acetone there was recovered 2.4 g. of yellow needles, melting at 92–93°.

Anal. Calc'd for $C_{16}H_{10}Br_6O_6$: Br, 59.0. Found: Br, 58.9.

Hydrogenolysis. By the Clemmensen procedure. Into a suitable apparatus was charged 45 g. of (III) in 1500 g. of glacial acetic acid. At 110° to 115°, zinc dust containing a trace of mercury was added slowly to provide continuous ebullition by the evolved hydrogen. These conditions were maintained for 52 hours, after which time the crude mixture was filtered hot to remove salts and unreacted zinc. On cooling, 35 g. of unchanged (III) was recovered by filtration. The filtrate was concentrated by stripping at 38–40° at 40 mm. The residue from this operation was a viscous liquid which slowly crystallized to a low-melting semi-solid mass. On storage at room temperature for five days, the crude product spontaneously changed to a high-melting solid. Fractional distillation produced 2.4 g. of substance identified as 2,6-dimethylpyrone, boiling at 130–132° at 14 mm., and melting at 131–132°.

The still residues from this distillation were recrystallized from water, giving 0.35 g. of a white crystalline product melting at 189–190°. This product was found by analysis and mixed melting point determinations with known material to be triacetic lactone.

By the Adkins procedure. In a series of experiments a three-liter pressure autoclave, equipped with an Aminco shaker mechanism and a heating jacket, was charged with acetic acid, Raney nickel, and (III). In each run the temperature of hydrogenation at a hydrogen pressure of 1000 p.s.i. was progressively increased to provide conditions of greater severity. The details are shown in Table I.

In each experiment the reaction mixture was discharged and filtered hot to remove the catalyst. Unchanged (III) was recovered by filtration on cooling and the filtrate fractionally distilled under low pressures, the distillate and the residues being examined for organic material other than solvent.

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[3] The authors are indebted to Dr. W. Swietoslawski and Dr. J. R. Anderson of Mellon Institute, Pittsburgh, Pa., for making available ebulliometric apparatus and for helpful advice.

[4] The authors are indebted to Wayne G. White, Carbide and Carbon Chemicals Corporation, South Charleston, West Virginia, for the experimental infrared absorption data.

In Runs 1 and 2, the starting material was recovered quantitatively.

In Run 3, there was obtained 0.85 gram of solid residue which, after recrystallization from acetone, yielded 0.35 g. of 2,6-dimethylpyrone.

Run 4 provided only slightly higher conversion with approximately 99 per cent of the starting material being recovered.

Under the more drastic conditions of Run 5 approximately 4 g. of the starting material was converted to other products. The residue from the distillation was taken up in hot methanol and cooled, giving a white solid. Recrystallization from methanol yielded 0.90 g. of dehydracetic acid, melting at 110–111°.

After the removal of the catalyst from the reaction mixture in Run 6 there was precipitated on cooling only 32 g. of the starting material. Low-pressure stripping of the solvent produced a residue of viscous tar which gradually solidified to a soft mush, badly discolored to a dark red. Distillation of this residue yielded only a trace of 2,6-dimethylpyrone. Decomposition prevented further exploration by this method. Fractional crystallization failed to yield an identifiable product.

Reduction with hydrogen iodide. A mixture of 10 g. of (III) and 200 g. of a 32% glacial acetic acid solution of hydrogen iodide containing a trace of red phosphorus was placed in a sealed tube of about 500 ml. capacity and heated for 48 hours at 150–155°. When cool, the tube was opened and excess hydrogen iodide and acetic acid removed by low-pressure stripping through a fractionating column. The tar-like residue, weighing 9.3 g., was incapable of resolution by solvent crystallization. Distillation produced 2 g. of 2,6-dimethylpyrone.

TABLE I

CONDITIONS OF HYDROGENOLYSIS: ADKINS PROCEDURE

RUN NO.	WEIGHT (IV) (G.)	WEIGHT ACETIC ACID (G.)	WEIGHT RANEY NI (G.)	TEMPERATURE °C.	TIME HRS.
1	30	1000	5	25	18
2	30	1000	5	75	10
3	30	1000	5	105	6
4	45	1500	8	120	10
5	30	1000	5	145	6
6	45	1500	8	200	12

This reduction was repeated at 175°, resulting in the formation of heavier tars and only a trace of the pyrone.

Oxidation. With nitric acid. Twenty grams of (III) was dissolved in 200 g. of concentrated nitric acid (70% by weight) at 20°. The solution was maintained at this temperature for 10 hours and then carefully diluted with ice water to ten times the initial volume, the temperature being maintained below 20° throughout the dilution. The starting material was recovered unchanged.

In a second experiment at 40–50° oxalic acid was obtained. This was determined quantitatively by the precipitation of its calcium salt. It was found that 10.30 g. of (III), equivalent to 6.71 g. of carbon, yielded 15.02 g. of calcium oxalate, equivalent to 2.818 g. of carbon. Thus 42% of the carbon in (III) is oxidizable to oxalic acid.

With peracetic acid. Oxidation of (III) was accomplished by treating 15 g. of the substance in 100 g. of glacial acetic acid with peracetic acid, prepared from 714 g. (7.0 moles) of acetic anhydride and 300 g. of 30% hydrogen peroxide (available peracetic acid 16.8% by weight). The reaction mixture was maintained at 100° for ten hours. No crystalline product precipitated on cooling. After removal of water and acetic acid by low-pressure stripping through a fractionating column there remained 2.6 g. of triacetic lactone, melting at 187–189°. A mixed melting point with known material was unchanged.

Hydrolysis with hydrochloric acid. A solution of 25 g. of (III) and 500 g. of glacial acetic

acid was heated to 95° and concentrated hydrochloric acid (36% in water) slowly added until the system was saturated with hydrogen chloride as judged by continuous ebullition by evolved excess hydrogen chloride. The reaction system was maintained for 35 hours at 98–100°. No solid phase separated on cooling. Excess hydrogen chloride, water, and acetic acid were removed by low-pressure stripping, yielding a balsam-like residue from which only the starting material could be isolated by selective solvent extraction. Low-pressure distillation produced a crystallizable distillate, boiling over a wide range. The distillate was recrystallized from water and 3.2 g. of triacetic lactone recovered.

General chemical characterization. Detecting the presence of functional groups was complicated by the extreme insolubility of the compound in common organic solvents. On testing the unknown substance (III) with the appropriate reagents the following facts were established.

a. It contains no carboxyl group, either as free acid or ester.
b. Iodoform test was negative.
c. Tollens Reagent and Fehling's Solution were not reduced.
d. Ferric chloride solution showed no significant coloration.
e. Phenylhydrazine failed to produce a phenylhydrazone under the usual conditions.
f. Chlorination by the action of phosphorus pentachloride or thionyl chloride only charred the compound to carbon.
g. It showed relatively high solubility in cold concentrated mineral acids; 70 per cent nitric acid, 98 per cent sulfuric acid, 85 per cent phosphoric acid, and 36 per cent hydrochloric acid. On dilution of these acid solutions with cold water the product was precipitated unchanged.
h. Aqueous alkali, aqueous ammonia, and organic amines dissolved the unknown substance while converting it to resinous tars.
i. It showed no susceptibility to nitration or sulfonation.
j. No unsaturation toward bromine at 20°C. in dilute solution was observed.

The reaction of diketene with 2-butanone. A mixture of 420 g. (5.0 moles) of diketene and 360 g. (5.0 moles) of methyl ethyl ketone, boiling at 79–80° (n_D^{20} 1.3786), was heated on a steam-bath at 95–100° for 250 hours.

Fractional distillation through a column of 20 theoretical plates at 5 to 1 reflux ratio yielded 11 g. of an unsaturated material distilling at 147–148° at 751 mm., d_{20}^{25} 0.8692. It gave a liquid oxime boiling at 96–97° at 10 mm., and on hydrogenation over Raney nickel at room temperature yielded 4-methyl-2-hexanone, *semicarbazone*, m.p. 105–106°.

The original unsaturated substance was thus identified as 4-methyl-3-hexene-2-one (17).

SUMMARY

The polymerization of diketene has been studied under alkali-catalyzed conditions.

Four previously unreported products have been isolated. They are carbon dioxide, acetone, 2,6-dimethylpyrone, and a heretofore unknown substance characterized as 2,6-bis-(6-methyl-4-oxo-2-pyranylmethyl)pyrone.

A mechanism is proposed by which these compounds may be formed from diketene and evidence in its support is discussed.

PITTSBURGH, PA.

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[Contribution from the Chemistry Laboratory of Furman University]

RATES OF PHOTOBROMINATION OF FLUORENE AND 2-METHYLNAPHTHALENE

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The enhanced effect of iodine as carrier in the dark-room bromination of fluorene (1) raises the question of its influence on the photobromination of this molecule (2). In the first part of the present paper it is shown that the presence of iodine reduces the formation of 9-bromofluorene in the photobromination. By the passage of light from a six-inch mercury arc through iodine filters, effects have been secured which range from no production of 9-bromofluorene to where all the bromination takes place in the 9-position.

A Coleman Universal Spectrophotometer, Model 14, has been used to extend the photochemical study. The effect of different wave lengths of monochromatic light on the bromination of fluorene and 2-methylnaphthalene in both carbon tetrachloride and carbon disulfide has been examined. 2-Methylnaphthalene was selected because of the strong tendency of the bromine to enter the favored 1-position of this molecule, rather than the side-chain.

EXPERIMENTAL

EFFECT OF IODINE ON THE PHOTOBROMINATION OF FLUORENE

In Table I the samples of fluorene (1.66 g.), dissolved in 10.00 ml. of carbon tetrachloride and 10.00 ml. of the same solvent containing the quantity of iodine indicated, were refluxed in an Erlenmeyer flask attached to a condenser by a ground-glass joint with a 6″ mercury arc placed ½″ from the flask; 10.00 ml. of molar bromine-carbon tetrachloride solution was added down the condenser; after 3 minutes the arc was cut off, excess sodium thiosulfate solution added to stop the bromination, and the carbon tetrachloride was separated, washed and analyzed for 9-bromofluorene by the sodium iodide method (3).

The presence of 0.2899 g. of iodine reduces markedly the formation of 9-bromofluorene even under the conditions of strong irradiation and high temperature. In order to determine if all the bromination took place in the 9-position in the presence of iodine, analyses were made on the same solutions both by the sulfite and sodium iodide methods.(Table II). Previous work (4) has shown that the former analysis gives the total bromination, while the latter gives the percent of 9-bromofluorene only. The experiments were made with one Mazda lamp (200W) at 3″ for 4 minutes in a thermostat at 41°.

From Table II it is apparent that 0.0289 g. iodine reduced the formation of 9-bromofluorene to one-third of the total bromination. How much of this effect was due to the absorption of the irradiation by the iodine in the solution? As an approach to this screening effect of iodine, the light from a 200-W Mazda bulb was passed through one and one-eighth inch of an iodine solution before reaching the flask containing 1.66 g. of fluorene in 20.00 ml. of pure carbon tetrachloride; the total distance of the bulb from the reaction flask was 3½″; the reaction time, 4 minutes at 41°.

Several interesting observations can be drawn from a comparision of Table II and III. The passage of light through the screen of pure carbon tetrachloride did not reduce the rate of bromination. The 0.0029 iodine filter slowed down the reaction, but strangely enough, all the bromine still entered the 9-position. On the other hand, the passage of light through the 0.0289 iodine filter reduced sharply the total bromination, and only one-

half of the bromine now entered the 9-position. When this same strength of iodine (0.0289 g.) was present in the reaction mixture, the total bromination was greater but only one-third of the bromine entered the 9-position. Finally, the 0.2899 iodine filter absorbed all the irradiation, for when several brominations were performed in a dark room at 41° for 4 minutes, the average was 12% bromination by the sulfite analysis and 0% bromination by the sodium iodide method for 9-bromofluorene.

TABLE I

FORMATION OF 9-BROMOFLUORENE IN THE PRESENCE OF IODINE

CONC. I_2 (G.)	9-BR-FL. %	CONC. I_2 (G.)	9-BR-FL. %	CONC. I_2 (G.)	9-BR-FL. %
0.2899	13	0.0289	77	0.0029	90
0.2899	10	0.0289	75	0.0029	90
0.2899	12				

TABLE II

AMOUNT OF 9-BROMOFLUORENE IN THE TOTAL BROMINATION WITH IODINE PRESENT, 41°, 200 W MAZDA LAMP

CONC. I_2 (G.)	9-BR-FL. (NAI ANAL.)	TOTAL BROM. (Na_2SO_3 ANAL.)
0.0289	12%	35%
0.0289	13%	34%
Pure CCl_4	70%	72%
Pure CCl_4	69%	72%

TABLE III

ABSORPTION OF IRRADIATION BY IODINE FILTERS

SOLUTION IN FILTER (G. PER 10.00 ML.)	9-BR-FLUORENE (NAI ANAL.) %	TOTAL BROMINATION (Na_2SO_3 ANAL.) %
0.2899	0	11
.0289	7	15
.0289	7	14
.0029	44	44
.0029	44	44
Pure CCl_4	69	70
Pure CCl_4	70	69

USE OF SPECTROPHOTOMETER

A Coleman Universal Spectrophotometer, Model 14, has been used to determine the effect of different wave lengths of monochromatic light on the bromination of fluorene and 2-methylnaphthalene, both with and without iodine present in the solvents, carbon tetrachloride and carbon disulfide. The instrument was adapted for temperature control by connecting the well in the same with a constant temperature bath. The spectrophotometer was set at a desired wave length with the galvanometer dials in full counterclockwise position. A cuvette containing 0.005 mole of purified hydrocarbon in 5.00 ml. solvent was placed in the cuvette well at 41°; 10.00 ml. $M/2$ bromine in carbon tetrachloride or carbon disulfide (0.005 mole) were added. Anhydrous conditions were maintained by having a calcium chloride tube on the outlet for the hydrogen bromide. After a given length of time

TABLE IV

PHOTOBROMINATION OF FLUORENE AND 2-METHYLNAPHTHALENE, 0.005 MOLE, 41°

EXPER.	IRRADIATION (A°)	EXPOSURE (MIN.)	IODINE (G.)	SOLVENT	TOTAL BROM. %	SIDE-CHAIN BROM. %
Effect of change in wave length with fluorene						
1- 4	3750	20	—	CCl_4	22.9	1.8[a]
5- 8	4250	20	—	CCl_4	23.7	3.1[a]
9	5000	20	—	CCl_4	24.2	13.5
10	5000	20	—	CCl_4	25.7	13.3
11-16	5250	20	—	CCl_4	31.4	15.4[a]
17-20	6250	20	—	CCl_4	26.2	9.3[a]
21-27	6750	20	—	CCl_4	21.2	2.1[a]
28	7500	20	—	CCl_4	17.4	0.9
29	7500	20	—	CCl_4	17.4	1.1
Change in solvent with fluorene						
30	3750	20	—	CS_2	22.9	1.8
31	3750	20	—	CS_2	23.8	1.8
32-35	5250	20	—	CS_2	21.7	5.1[a]
36-39	6750	20	—	CS_2	22.0	2.6[a]
Iodine effect with change of solvent and time of irradiation of fluorene						
40-43	5250	20	0.0015	CCl_4	58.5	1.7[a]
44-47	5250	20	0.0002	CCl_4	29.5	9.3[a]
48	5250	5	—	CCl_4	20.3	6.7
49	5250	5	—	CCl_4	20.5	5.5
50	5250	3	—	CCl_4	19.1	3.7
51	5250	3	—	CCl_4	18.6	3.5
52-55	5250	1	—	CCl_4	20.5	3.2[a]
56-59	5250	3	—	CS_2	18.6	2.1[a]
60-63	5250	3	0.0002	CCl_4	24.0	2.2[a]
Change in wave length with 2-methylnaphthalene						
64	3600	20	—	CCl_4	43.3	3.3
65	3600	20	—	CCl_4	43.5	3.0
66	4250	20	—	CCl_4	31.5	5.2
67	4250	20	—	CCl_4	31.5	4.6
68-71	5250	20	—	CCl_4	34.7	6.7[a]
72	6000	20	—	CCl_4	41.6	4.0
73	6000	20	—	CCl_4	38.4	5.1
Iodine effect on 2-methylnaphthalene						
74-77	5250	20	0.0015	CCl_4	54.1	3.9[a]

[a] Average of number of experiments indicated.

the reaction was stopped by pouring the contents of the cuvette into 15.00 ml. $M/2$ sodium sulfite-sodium acetate solution, and the excess was titrated with $M/4$ iodine solution to determine the percent of total bromination. A sodium iodide analysis (4) on the residue from the carbon tetrachloride layer gave the percent of active bromine (9-bromofluorene

or 2-bromomethylnaphthalene) formed during the reaction. All experiments were run for 20 minutes; in a number of experiments the reaction was exposed for the time indicated in column 3 of Table IV to the wave length given in column 2; the irradiation was always done at the beginning of the 20 minutes period.

DISCUSSION OF RESULTS

Effect of change in wave length on the rates of photobromination. Four decades ago Bruner (5) determined with the aid of filters that yellow and green light (5000–5800 Å) was more effective in side-chain bromination of toluene in carbon tetrachloride. Four years later LeBlanc and Andrich (6) reported a constant rate of photobromination of toluene between the wave lengths 3270–5790 Å when the reaction was carried out in an atmosphere of oxygen. The next year these authors (7) published a series of three articles on the photobromination of toluene: they reported that the more oxygen present, the higher the yield of benzyl bromide, and they confirmed the constant yield of benzyl bromide between 3250–5790 Å; finally, they found the reaction rate decreased rapidly below 4000 Å and that it was not light sensitive between 2000 and 3000 Å.

Our results show that the photobromination of fluorene and 2-methylnaphthalene differ from the above picture for toluene in several ways. An examination of Table IV reveals that the total bromination of fluorene was little influenced by change in wave length from 3750–7500 Å; (Exper. 1–29), but that the rate of formation of 9-bromofluorene, corresponding to side-chain bromination, increased seven-fold up to 5250 Å and then dropped off again with continued increase in wave length. And our data reveal (Exper. 64–73) that the photobromination of 2-methylnaphthalene resulted chiefly in nuclear bromination, and neither the nuclear nor the side-chain reaction was influenced markedly by change in wave length, although the latter did reach a definite peak at 5250 Å. Kozak (8) reported a maximum rate at 5160 Å.

Effect of change in solvent. The rate of photobromination of fluorene in carbon disulfide followed the same general pattern as that in carbon tetrachloride (Exper. 30–39), except the peak of 9-bromofluorene formation at 5250 Å was only about one-fourth that in carbon tetrachloride. The rates for total bromination and for formation of 9-bromofluorene were almost identical for the two solvents at the extremes of 3750 and 6750 Å.

Iodine effect with change in solvent and time of irradiation. The literature on the use of iodine in photobrominations is not extensive, although this carrier has been employed widely in non-photobrominations. In 1875 Jannasch (9) obtained only ring bromination when he used 25 g. iodine and 100 g. bromine in the bromination of toluene in sunlight. Bruner (10) added traces of iodine to destroy the "after effect" in the photobromination of toluene; he secured high yields of benzyl bromide by using high ratios of toluene to bromine (up to 200 to 1). Kharasch (11) explains these "after effects" as due to the presence of peroxides, which are removed by the addition of such reagents as iodine, hydrogen bromide and excess toluene[1].

[1] Neither fluorene nor 2-methylnaphthalene gave a positive test for peroxides when our purified samples were tested by Nozaki's method (12).

Brewster (13) and Hopper (14) have employed a crystal of iodine in their photochemical preparations of *p*-nitrobenzyl bromide.

The presence of 0.0015 g. iodine in the bromination of fluorene in carbon tetrachloride with 20 minutes exposure to 5250 Å almost doubled the rate of total bromination, but it decreased the formation of 9-bromofluorene to one-tenth its value in pure carbon tetrachloride (Exper. 11–16, 40–43). On the other hand, 2-methylnaphthalene showed an increase of about 50% in nuclear bromination and a corresponding decrease in side-chain bromination in the presence of the same iodine concentration (Exper. 68–71, 74–77).

The photobromination of fluorene showed some "after effect" in the absence of iodine, for reducing the time of irradiation at 5250 Å to five minutes cut the rate of total bromination to two-thirds and the formation of 9-bromofluorene to about one-third the value for the 20 minute irradiation (Exper. 11–16, 48–49). With only 1 minute of irradiation, the rate of total bromination remained the same as for 5 minutes, but there was only one-fifth the amount of 9-bromofluorene formed (Exper. 48–49, 52–55).

ACKNOWLEDGMENTS

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SUMMARY

1. The presence of iodine reduced the amount of 9-bromofluorene found during the photobromination. By the passage of light from a 6″ mercury arc through a series of filters, effects have been produced which range from no production of 9-bromofluorene to those where all the bromination took place in the 9-position.

2. With the aid of a Coleman Universal Spectrophotometer the following facts characterized the photobromination of the two hydrocarbons under investigation in 0.005 *M* solution:

a. The total bromination of fluorene was little influenced by a change in wave length from 3750–7500 Å, but the rate of formation of 9-bromofluorene increased sevenfold to a maximum at 5250 Å.

b. The rate of formation of 9-bromofluorene and the rate of total bromination of this molecule were about the same in the two solvents, carbon tetrachloride and carbon disulfide, at the extremes of 3750 and 6750 Å. But at 5250 Å the rate of formation of 9-bromofluorene in the latter solvent was only about one-fourth of that obtained in carbon tetrachloride.

c. The photobromination of 2-methylnaphthalene resulted chiefly in nuclear bromination, but with a definite peak at 5250 Å for side-chain bromination.

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[Contribution from the Sterling Chemistry Laboratory, Yale University]

THIOPHANE-2,5-DICARBOXYLIC ACID AND RELATED COMPOUNDS[1]

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Received December 29, 1948

The disclosure in 1942 of the structure of biotin (1) aroused interest in the comparatively unexplored field of thiophane chemistry. One method of preparation of thiophane compounds has been the reaction between substituted 1,4-dihalobutanes and an alkali metal sulfide in aqueous or alcoholic solution.

$RCHXCH(R^1)CH(R^2)CHXR^3 + M_2S \rightarrow$  $+ \ 2MX$

Thiophane (2, 3, 4), methylthiophanes (4), 2,5- and 3,4-di-*n*-propylthiophanes (5), 3,4-dihydroxythiophane (6), and thiophane-2,5-dicarboxylic acid (7) have been prepared by this method. Recently, Kilmer and McKennis (8) used a variation of the above reaction in the preparation of 3,4-diaminothiophane by treatment of 2,3-diaminobutane-1,4-disulfuric acid with sodium sulfide.

The authors have extended the cyclization reaction to *meso*-ethyl 2,5-dibromoadipate (9) and have prepared *cis*-2,5-dicarbethoxythiophane (10) in good yield. The cyclization was found to be sensitive to different conditions and media. If the amount of sodium sulfide was in great excess or if the reaction was carried out at elevated temperatures, the secondary reaction of hydrolysis was greatly promoted. The most suitable diluent for cyclization was ethanol, and indeed other common organic solvents were found to be unsatisfactory. When small amounts of potassium iodide were tried as catalyst, the yield of the thiophane ester was increased.

Cis-2,5-dicarbethoxythiophane was found to be unexpectedly sensitive to reagents. In hot concentrated caustic solution, there is apparently some cleavage of the sulfide linkage, and the yield of thiophane-2,5-*cis*-dicarboxylic acid by saponification is unsatisfactory. However, in acid solution, the hydrolysis proceeded smoothly and with good yield. The dibasic acid had similar properties to the thiophane-2,5-*cis*-dicarboxylic acid described by Fredga (7) and Brown and Kilmer (10). It has been proved beyond doubt (7) that the carboxyl groups had a *cis* structure. The *cis* diacid formed an anhydride when its salt was treated with thionyl chloride.

By treatment of *cis*-2,5-dicarbethoxythiophane with aqueous ammonia after the following equilibrium had been established by means of sodium methylate in

[1] Abstracted from the doctoral dissertation presented by Richard J. Turner to the Faculty of the School of Graduate Studies of Yale University.

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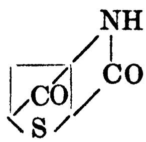
methanol solution, according to the procedure of Sessions (11), 2,5-dicarbamylthiophane was obtained.

$$RCO_2C_2H_5 + CH_3OH \rightleftarrows RCO_2CH_3 + C_2H_5OH$$

In view of the work by Baker, Brown, and associates (12, 13), a *trans* structure may be assigned to the diamide because of the inversion of a *cis* to a *trans* form due to the sodium methylate.

The *trans*-amide underwent dehydration in the presence of phosphorus pentachloride to form the corresponding *trans*-nitrile. However, when *trans*-2,5-dicarbamylthiophane was treated with phosphorus oxychloride, a cyclic imide (I) was obtained.



(I)

A *cis* structure is assigned to the imide in view of a similar transformation noted by Baker and co-workers (14), in which a *trans*-amide, 2-(δ-carboxybutyl)-4-carbanilidothiophane-3-*trans*-carboxylic acid, was converted to a *cis*-imide, namely, 2-(δ-carboxybutyl) thiophane-3,4-*cis*-dicarboxanil.

The *cis*-imide was found to be similar to phthalimide in its reactions with alkyl halides. For example, an excellent yield of N-(n)-amylthiophane-2,5-dicarboxylic acid imide was obtained when the sodium salt of the imide was treated with n-amyl bromide.

When 2,5-dicarbamylthiophane was submitted to the Hofmann rearrangement in the presence of sodium hypobromite, there was complete sulfide cleavage and destruction of the thiophane nucleus. This is in agreement with the observations of Brown and Kilmer (10) who attempted the synthesis of 2,5-diaminothiophane by the hydrolysis of a 2,5-bis-(carbethoxyamino)thiophane. These investigators noted a similar cleavage and commented on the instability of compounds of the general type: $RSCH(NH_2)R^1$.

Cis-2,5-dicarbethoxythiophane was transesterified with 2-diethylaminoethanol and 3-diethylaminopropanol to yield the corresponding bis-alkamine esters. In view of the fact that the transesterification was carried out in the presence of a sodium alcoholate, the products are equilibrium *trans-cis* mixtures.

EXPERIMENTAL

Cis-2,5-dicarbethoxythiophane (10). A mixture of 36 g. (0.1 mole) of *meso*-ethyl 2,5-dibromoadipate (9), 200 cc. of 95% ethyl alcohol, 30 g. (0.125 mole) of sodium sulfide (nonahydrate), and 2 g. of potassium iodide was stirred at room temperature for six hours. The alcohol was removed *in vacuo* and the residue, acidified with sulfuric acid, was extracted with ether. The ether extracts were washed with sodium thiosulfate solution and with water. The oil obtained, after removal of the ether, distilled at 100° at 0.3 mm. and weighed 16.5 g. (71%); n_D^{25} 1.4808.

Anal. Calc'd for $C_{10}H_{16}O_4S$: S, 13.79. Found: S, 13.56.

Trans-2,5-dicarbamylthiophane. To 30 cc. of methanol containing a small piece of dissolved sodium was added 23.2 g. (0.1 mole) of *cis*-2,5-dicarbethoxythiophane and the mixture was allowed to come to equilibrium in a stoppered flask at room temperature for eighteen hours. At the end of this time, 125 cc. of concentrated aqueous ammonia (sp. g., 0.9) was added and after the mixture was thoroughly agitated, it was placed in the cold for one week. The white solid which had precipitated was collected, washed with ether and dried. The yield was 12.8 g., m.p. 179–181°. The concentrated filtrate furnished 2.5 g. more, raising the total yield to 15.3 g. (88%).

Anal. Calc'd for $C_6H_{10}N_2O_2S$: N, 16.08. Found: N, 15.92.

Thiophane-2,5-cis-dicarboxylic acid (*7, 10*). A mixture of 23.2 g. (0.1 mole) of *cis*-2,5-dicarbethoxythiophane, 140 cc. of water, 20 cc. of concentrated sulfuric acid, and 70 cc. of glacial acid was heated under reflux for twelve hours. The solution was concentrated *in vacuo* and the white solid which precipitated was collected, washed with ether, and dried. The yield was 13.5 g. (76.7%); m.p. 135–136°. Fredga (7) reported a melting point of 144–145°.

Anal. Calc'd for $C_6H_8O_4S$: S, 18.19. Found: S, 18.30.

The anhydride of thiophane-2,5-dicarboxylic acid. Seven and two-tenths grams (0.035 mole) of the sodium salt of thiophane-2,5-*cis*-dicarboxylic acid, prepared by the addition of sodium ethylate to an alcohol solution of the dibasic acid, was added to a mixture of 2.14 g. (0.018 mole) of thionyl chloride and 55 cc. of acetic anhydride in a round-bottom flask equipped with a condenser, fitted with a calcium chloride tube, and a mechanical stirrer. The mixture was heated on a water-bath at 70° for two hours. A small amount of solid matter was filtered off and the filtrate was evaporated under diminished pressure. The darkly colored residue was taken up in hot nitromethane, treated with Norit, and filtered. The concentrated filtrate yielded 1.25 g. (22.6%) of transparent rods and plates, m.p. 141–142°.

Anal. Calc'd for $C_6H_6O_3S$: C, 45.55; H, 3.82; S, 20.26.
Found: C, 45.55; H, 4.03; S, 20.00.

The imide of thiophane-2,5-cis-dicarboxylic acid. In a small distilling-flask connected to a receiver was placed 8.7 g. (0.05 mole) of *trans*-2,5-dicarbamylthiophane and 20 cc. (0.217 mole) of phosphorus oxychloride. The mixture was heated on a steam-bath for one and one-half hours and the excess phosphorus oxychloride was then removed under diminished pressure. Water was added to the chilled residue, and when all evidence of an oil had disappeared, the solid imide was filtered and washed with water. The yield was 6.4 g. (81.6%); m.p. 145–146°.

Anal. Calc'd for $C_6H_7NO_2S$: N, 8.91; S, 20.39.
Found: N, 8.95; S, 20.36.

N-(n)-Amylthiophane-2,5-dicarboxylic acid imide. In a three-necked flask, equipped with a mechanical stirrer, a condenser protected with a calcium chloride tube, and a dropping-funnel, were placed 10.24 g. (0.32 mole) of dry methanol and 0.92 g. (0.04 g. atom) of sodium. When the sodium had dissolved, 6.28 g. (0.04 mole) of thiophane-2,5-dicarboxylic acid imide was introduced, and while the solution was chilled in an ice-bath, 11.6 g. (0.77 mole) of freshly distilled *n*-amyl bromide was added dropwise. The solution was allowed to come to room temperature slowly and then heated for one hour at 60° and for four hours at 80–90°. The solution then gave a negative test with moist red litmus paper. The solvent was distilled *in vacuo*, and the residue was dissolved in ether. The filtered ether solution was evaporated to a syrup, which was crystallized from 10% aqueous ethanol. The crystallizate weighed 7.4 g. (81%); m.p. 52°. After two recrystallizations from dilute ethanol the m.p. was 68°, unchanged by further crystallization.

Anal. Calc'd for $C_{11}H_{17}NO_2S$: N, 6.16. Found: N, 6.09.

Trans-2,5-dicyanothiophane. An intimate mixture of 8.7 g. (0.05 mole) of *trans*-2,5-dicarbamylthiophane and 24.4 g. (0.117 mole) of phosphorus pentachloride was placed in a distilling-flask which was attached to a condenser. The reactants were heated at 115–120° for one and one-half hours, and at the end of this time, the darkly colored residue was ex-

tracted several times with ether. The united ether extracts were washed with sodium bicarbonate and with water. The dried ether solution was distilled, first at atmospheric pressure, and finally *in vacuo*. A fraction of b.p. 124°/1 mm. crystallized in the form of fine, colorless needles; weight, 0.80 g. (11.6%); m.p. 87° after recrystallization from dilute alcohol.

Anal. Calc'd for $C_6H_8N_2S$: N, 20.29. Found: N, 20.46.

The sulfone of cis-2,5-dicarbethoxythiophane. A mixture of 5.8 g. (0.025 mole) of *cis*-2,5-dicarbethoxythiophane, 25 cc. of glacial acetic acid, and 15 cc. of 30% hydrogen peroxide were placed in a small stoppered flask and allowed to stand at room temperature for eight days. The solvent was then removed under diminished pressure and the oil that remained was distilled, b.p. 155°/1 mm.; n_D^{25} 1.4790. The distillate crystallized in the form of colorless flaky plates, m.p. 40°; yield, 2.7 g. (41%).

Anal. Calc'd for $C_{10}H_{16}O_6S$: S, 12.13. Found: S, 12.00.

2,5-bis-(3-Diethylaminocarbopropoxy)thiophane. Eighty-five and fifteen one-hundredths grams (0.65 mole) of 3-diethylaminopropanol, containing a small amount of dissolved sodium, was added to 11.6 g. (0.05 mole) of *cis*-2,5-dicarbethoxythiophane, and the mixture was heated at 165–170° for seven hours. At the end of this time, the excess 3-diethylaminopropanol was removed under diminished pressure, and the residue was extracted with several portions of ether. The united extracts were shaken with saturated sodium chloride solution, dried with calcium chloride, and evaporated. The residual oil was resubmitted to transesterification in the manner just described. Repetition of the isolation procedure gave a colorless distillate; b.p. 195–197°/1 mm.; weight 3.0 g. (15%); n_D^{25} 1.4840.

Anal. Calc'd for $C_{20}H_{38}N_2O_4S$: N, 6.95. Found: N, 6.65.

2,5-bis-(2-Diethylaminocarbethoxy)thiophane. This ester was prepared in a manner similar to that described for 2,5-bis-(3-diethylaminocarbopropoxy)thiophane. From 76 g. of 2-diethylaminoethanol and 11.6 g. (0.05 mole) of *cis*-2,5-dicarbethoxythiophane was obtained 5.0 g. (26.7%) of product; b.p. 177–179°/0.75 mm.; n_D^{25} 1.4858.

Anal. Calc'd for $C_{18}H_{34}N_2O_4S$: N, 7.48. Found: N, 7.33.

SUMMARY

The condensation of *cis*-ethyl 2,5-dibromoadipate with sodium sulfide to yield *cis*-2,5-dicarbethoxythiophane has been studied.

The products obtained by treatment of *cis*-2,5-dicarbethoxythiophane and related compounds with a variety of reagents are reported.

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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE OHIO STATE UNIVERSITY]

ATTEMPTED SYNTHESIS OF THE OPTICAL ISOMERS OF 2,3-DIMETHYLCHOLANTHRENE.[1]

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The desirability of synthesizing optically active carcinogens has been mentioned previously by Fieser and Seligman (1) who prepared 2,3-dimethylcholanthrene, III, (16,20-dimethylcholanthrene by their numbering system) for this purpose, but did not attempt to resolve it. Subsequently, this hydrocarbon was shown to be an active carcinogen when tested on mice (2). We have taken up this problem[3] and report herein attempts to obtain the optical antipodes of 2,3-dimethylcholanthrene, III.

Since we knew of no good method for the resolution of III, we resolved the intermediate 1,7-dimethyl-4-hydrindenecarboxylic acid, I, converted it into active 1,7-dimethyl-4-(1-naphthoyl)hydrindene, II, and subjected II to pyrolysis at 400–420°. The resulting hydrocarbon, III, was largely, if not completely, racemized. Accordingly, this line of attack was abandoned and the inactive ketone, II, was converted to III by pyrolysis as above. It was hoped that resolution of III could be accomplished by introducing a carboxy or amino group, resolving, and then removing the functional group. A monocarboxylic acid was prepared in good yield by acetylation followed by hypochlorite oxidation, but we were unable to resolve the acid thus produced. Nitration gave in poor yield a dinitro derivative.

Attempts to resolve III by preparing an optically active polynitro compound capable of forming a complex with III are under way in this laboratory.

EXPERIMENTAL[4]

4-Chloro-7-methylhydrindone. After condensation of 385 g. each of *p*-chlorotoluene and β-chloropropionyl chloride as described (3), the crude mixture of hydrindones after a charcoal treatment was allowed to crystallize from 1 liter of benzene. Most of the 4-methyl-7-chlorohydrindone, 176 g. (35%), m.p. 122–125° after sintering at 116°, crystallized and the remaining product was vacuum-distilled to yield 165 g. (33%) of colorless 4-chloro-7-methylhydrindone, b.p. 124–130° at 4 mm., which soon crystallized to a solid, m.p. 73–77°.

4-Chloro-1,7-dimethylindene. A solution of 329 g. (1.82 mole) of 4-chloro-7-methylhydrindone in 1 l. of benzene and 500 cc. of ether was added during 90 minutes to a stirred, refluxing Grignard solution prepared from 517 g. (3.64 mole) of methyl iodide in 1.5 l. of ether. After 3 more hours the mixture was treated with ice and hydrochloric acid and the ethereal solution washed with sodium thiosulfate solution. No separate treatment was

[1] The work herein reported is taken from the Ph.D. thesis of Jack Linsk, Ohio State University, June, 1948.

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[3] Professor Fieser informed us that he was no longer pursuing this research.

[4] All melting points are corrected. Analyses marked [o] by Oakwold Laboratories, Alexandria, Va.; [p] by J. Polglase, O. S. U.; [k] by Mrs. E. Klotz, O. S. U.; and [s] by S. Sadtler and Sons, Philadelphia, Pa.

necessary to dehydrate the carbinol. The indene was obtained as a colorless liquid, b.p. 102–103° at 1.8 mm., $n_D^{[illegible]}$ 1.5774, in 85.5% yield.

Anal.[o] Calc'd for $C_{11}H_{11}Cl$: C, 73.9; H, 6.2.
Found: C, 74.0; H, 6.3.

4-Chloro-1,7-dimethylhydrindene. In a typical experiment, a mixture of 119 g. of the pure, freshly distilled indene, 50 cc. of absolute alcohol, and 0.5 g. of Adams' platinic oxide catalyst was shaken under 3–2 atmospheres pressure of hydrogen. Reduction was complete in one hour and 113 g. (94%) of 4-chloro-1,7-dimethylhydrindene, b.p. 73–74° at 1 mm., $n_D^{[illegible]}$ 1.5411, was obtained as a colorless liquid.

Anal.[o] Calc'd for $C_{11}H_{13}Cl$: C, 73.1; H, 7.3.
Found: C, 73.2; H, 7.1.

4-Cyano-1,7-dimethylhydrindene. The above chloro compound was converted into the cyano compound, b.p. 114–118° at 1.6 mm., in 88% yield using a procedure similar to that previously described (3). Redistillation for analysis yielded a sample, b.p. 105–106° at 0.6 mm., $n_D^{[illegible]}$ 1.5489.

Anal.[p] Calc'd for $C_{12}H_{13}N$: C, 84.2; H, 7.7.
Found: C, 84.4; H, 7.8.

1,7-Dimethyl-4-hydrindenecarboxamide. A solution of 0.5 g. of the nitrile in 2 cc. of concentrated sulfuric acid was heated to 95°, cooled, and poured on ice. The amide, m.p. 148–150°, was obtained in 63% yield. A sample recrystallized for analysis melted at 151–152°.

Anal.[p] Calc'd for $C_{12}H_{15}NO$: N, 7.4. Found: N, 7.3.

1,7-Dimethyl-4-hydrindenoic acid. I. To a solution of 13.7 g. of nitrile in 35 cc. of concentrated sulfuric acid which had been heated to 105° and cooled was added a solution of 35 cc. of water and 70 cc. of acetic acid and the whole refluxed for fifteen hours. The solids were collected and the acid taken into alkali, treated with decolorizing charcoal, and precipitated with acid. On recrystallization from aqueous methanol 91 g. (60%) of acid, m.p. 175.5–177°, was obtained as colorless needles. A sample recrystallized for analysis melted at 177.0–178.0°.

Anal.[p] Calc'd for $C_{12}H_{14}O_2$: C, 75.8; H, 7.4.
Found: C, 75.8; H, 7.3.

Resolution of I. A solution containing 16.4 g. of racemic I and 28.1 g. of quinidine, m.p. 171.1–171.5° (purified by liberation from the sulfate and crystallization from methanol), was refluxed for one hour and treated with 150 cc. of ether. Crystallization began on cooling and seeding [the first crystal was obtained after ten days from an ether-petroleum ether (b.p. 65–70°, Skellysolve B) mixed solvent]. The first crop, m.p. 169–174°, $[\alpha]_D^{[illegible]}$ 155.2°, weighed 24.8 g. After six recrystallizations from chloroform-ether solutions, the last two of which yielded salt having the same rotation, 9.7 g. (44%) of salt, m.p. 181.4–182.8°, $[\alpha]_D^{[illegible]}$ 131.5° ± 0.4°, (*c*, 2.65% in chloroform, 2 dm. tube) was obtained.

Anal.[s] Calc'd for $C_{32}H_{38}N_2O_4$: C, 74.7; H, 7.4.
Found: C, 74.8; H, 7.7.

The free acid was liberated from the salt with hydrochloric acid and was crystallized from chloroform-Skellysolve B to yield the *l*-isomer, m.p. 136.2–137.0°, (racemic form, m.p. 177–178°), $[\alpha]_D^{27}$ −47.8° ± 0.2° (*c*, 2.6% in chloroform, 2 dm. tube). The over-all yield of resolved *l*-acid varied from 22 to 30% in several experiments.

When 0.4 g. of the optically active acid was sealed in a Pyrex ampoule and heated at 380–390° for twenty minutes it was partly racemized and partly decarboxylated. On recrystallization 230 mg. of acid, m.p. 155–170°, $[\alpha]_D^{[illegible]}$ −18°, was obtained.

1,7-Dimethyl-4-(1-naphthoyl)hydrindene, II. Racemic and levo forms. This ketone (1) was prepared from 1-naphthylmagnesium bromide and 4-cyano-1,7-dimethylhydrindene as a viscous oil, b.p. 220–225° at 1.5 mm., in 90% yield by a method used for a closely related compound (3). No attempt was made to crystallize this ketone; it was pyrolyzed to III as described below.

To prepare optically active II, the Grignard reagent from 10.4 g. (0.05 mole) of 1-bromo-

naphthalene in 75 cc. of ether was treated with 4.58 g. (0.025 mole) of finely divided cadmium chloride. After stirring and warming for one hour, 20 cc. of benzene was added and to this was added during 15 minutes a solution of the acid chloride, prepared from 2.6 g. (0.014 mole) of *l*-acid, I, and purified (4) thionyl chloride, in 50 cc. of benzene. The mixture was stirred and held at reflux for one hour and the neutral fraction of the hydrolyzed reaction product was distilled at 0.3 mm to yield 4.0 g. (97%) of an amber viscous oil. Crystallization from Skellysolve B yielded the pure *l*-ketone, II, as colorless plates, m.p. 124.0–125.8° [the racemic ketone (1) melted at 112–114°], $[\alpha]_D^{24}$ −132.2° ± 1°, (*c*, 0.98% in chloroform, 2 dm. tube).

Anal.[c] Calc'd for $C_{22}H_{20}O$: C, 88.0; H, 6.7.

Found: C, 88.1; H, 6.5.

2,3-Dimethylcholanthrene, III. The hydrocarbon was obtained pure, *i.e.*, m.p. 169–170° (1), in 13.4% yield by heating 21.4 g. of the above described viscous ketone (racemic) at 400–415° for 20 minutes. Purification was effected mainly by recrystallization of the picrate. In a similar experiment with 2.18 g. of *l*-ketone (see above) there was isolated 0.2 g. (10%) of III, m.p. 165.6–167.2°, after more extensive purification. This material had possibly a very slight levo rotation but, since this experiment was so unpromising, we made no further attempt at pyrolysis. If a way could be found to lower the temperature of the Elbs reaction, possibly the active ketone would yield active hydrocarbon.

Complexes were prepared from III and several polynitro compounds. The *trinitrotoluene complex* formed red elongated plates from benzene, m.p. 152.6–154.4°.

Anal.[c] Calc'd for $C_{29}H_{23}N_3O_6$: C, 68.4; H, 4.6; N, 8.2.

Found: C, 68.5, 68.9; H, 4.3, 4.4; N, 7.9, 8.1.

The *trinitrofluorenone complex* (5), greenish-black crystals from a large volume of benzene, m.p. 235–239.5°, contained benzene of crystalization.

Anal.[k] Calc'd for $C_{35}H_{23}N_3O_7 \cdot C_6H_6$: N, 6.2. Found: N, 6.1.

The *2,4,2′,4′-tetranitrobiphenyl complex* was formed with more difficulty and contains two molecules of the biphenyl to one of III. It formed small red plates from methanol, m.p. 145.8–147.2°.

Anal.[k] Calc'd for $C_{46}H_{30}N_8O_{16}$: C, 58.1; H, 3.2; N, 11.8.

Found: C, 58.1, 58.4; H, 3.3, 3.5; N, 11.1, 11.4.

?-Acetyl- and ?-carboxy-2,3-dimethylcholanthrene. To a solution of 1.10 g. of III and 0.34 g. of acetyl chloride in 5 cc. of carbon disulfide and 15 cc. of nitroethane was added 0.85 g. of aluminum chloride during ten minutes. After one hour at room temperature the mixture was treated with dilute hydrochloric acid and the organic solvents were removed by steam distillation. The reaction products were taken into benzene and passed through a short chromatographic column of alumina. The eluate was concentrated to 20 cc. and further chromatographed to yield a total of 836 mg. of yellow needles, m.p. 173–180° (70% based on III not recovered) and 66 mg. of III. A sample recrystallized from benzene for analysis melted at 178.6–180.4°.

Anal.[k] Calc'd for $C_{24}H_{20}O$: C, 88.8; H, 6.2.

Found: C, 88.5; H, 5.9.

A solution of 0.5 g. of acetyl compound in 120 cc. of pyridine was treated with 75 cc. of a solution of potassium hypochlorite (containing a small excess) during 15 minutes. The temperature rose to 36°. After standing at room temperature for one hour, the mixture was poured into water containing 5 cc. of acetone to destroy excess oxidizing agent. Acidification after fifteen minutes afforded 469 mg. (93%) of acid, m.p. 285–295°, which was insoluble in hot aqueous alcoholic sodium hydroxide. Recrystallization was effected from a large volume of hot toluene and yielded a yellow microcrystalline solid.

Anal.[k] Calc'd for $C_{23}H_{18}O_2$: C, 84.1; H, 5.6.

Found: C, 84.1; H, 5.6.

Decarboxylation by refluxing for one hour in quinoline containing copper-bronze powder yielded III.

Attempts to resolve this acid with the aid of quinidine, brucine, cinchonine, and strychnine failed. The only crystalline product obtained was acid.

Dinitro-2,3-dimethylcholanthrene. A solution of 223 mg. of III in 12 cc. of benzene was treated with 0.2 cc. of concentrated nitric acid in 2 cc. of acetic acid, the temperature being maintained at 0–5° for 42 hours. The reaction product was crystallized once from aqueous acetone and three times from chloroform-petroleum ether, b.p. 65–70°, to yield a few milligrams of small orange needles, m.p. 215–218.5°.

Anal.[k] Calc'd for $C_{22}H_{16}N_2O_4$: N, 7.5. Found: 7.4.

SUMMARY

The synthesis of 2,3-dimethylcholanthrene by an improved procedure is described. The Elbs reaction on an optically active ketone intermediate leads to an optically inactive hydrocarbon.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

SOME 4,8-DIAMINOQUINOLINES[1]

CHARLES C. PRICE,[2] E. W. MAYNERT,[3] AND VIRGIL BOEKELHEIDE[4]

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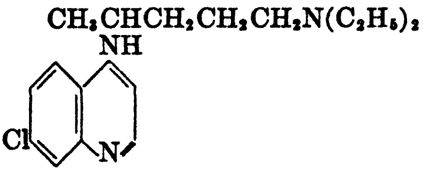
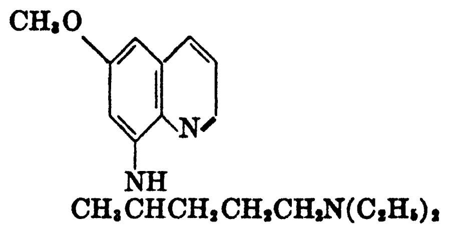
Certain 4-aminoquinolines, especially those bearing a 7-chlorine atom, such as Chloroquine (I), have value as antimalarial drugs (1). The preparation of compounds of this type, containing in addition an amino group in the eight position, was undertaken in the hope that the amino group might add some of the desirable pharmacological characteristics of Pamaquine (II). The compounds selected for preparation were the 6-methoxy and the 7-chloro derivatives of 8-amino-4-(4-diethylamino-1-methylbutyl)aminoquinoline.



I



II

The preparation of the 7-chloro compound was carried out in the following manner. Nitration of 4,7-dichloroquinoline (III) gave 4,7-dichloro-8-nitroquinoline (IV) in 90% yield. The 4,7-dichloro-8-nitroquinoline was reduced by treatment with iron and aqueous acetic acid to give 8-amino-4,7-dichloroquinoline (V) in 88% yield. When the 8-amino-4,7-dichloroquinoline was treated with an excess of 4-amino-1-diethylaminopentane and the mixture heated at 180° for ten hours, the desired 8-amino-7-chloro-4-(4-diethylamino-1-methylbutyl)aminoquinoline (VI) was formed in 67% yield.

In order to prove that the nitration and reduction had occurred as expected, a portion of the 8-amino-4,7-dichloroquinoline was converted by catalytic hydrogenation to 8-amino-7-chloroquinoline (VII). The 8-amino-7-chloroquinoline thus obtained was shown to be identical with an authentic sample (2) by the method of mixed melting points.

8-Amino-4-chloro-6-methoxyquinoline was prepared by reduction of the corresponding nitro compound (4), but it failed to couple with 4-amino-1-diethylaminopentane under the conditions tried.

[1] The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Illinois.

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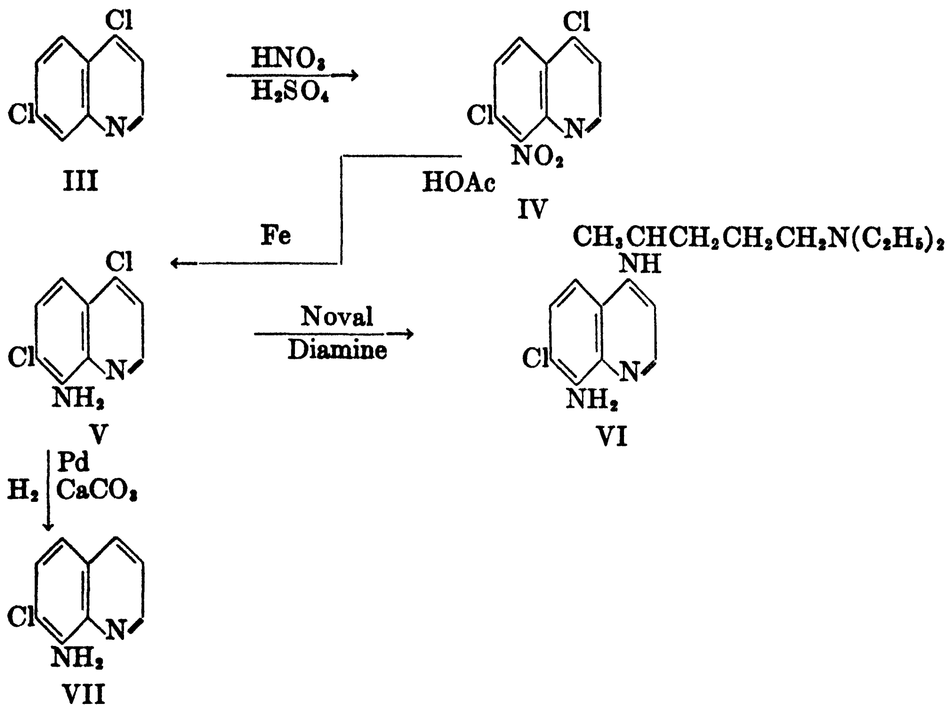

EXPERIMENTAL[5]

4,7-Dichloro-8-nitroquinoline (*IV*). Technical nitric acid (30 ml.) was added slowly to a solution of 4,7-dichloroquinoline (3) (19.8 g., 0.1 mole) in concentrated sulfuric acid (25 ml.) cooled in an ice-bath. The temperature was allowed to rise slowly until room temperature was reached and then the mixture was heated on a steam-bath for nine hours. After the mixture had cooled, it was poured over cracked ice. The yellow solid that precipitated was collected on a filter and washed with water. There was obtained 22.0 g. (90%) of crude product which melted at 148–149°. Crystallization of a sample from ethanol yielded light yellow plates that melted at 150–151°.

Anal. Calc'd for $C_9H_4Cl_2N_2O_2$: C, 44.48; H, 1.66.
Found: C, 44.88; H, 1.72.

8-Amino-4,7-dichloroquinoline (*V*). A mixture of the crude 4,7-dichloro-8-nitroquinoline (30 g., 0.12 mole) and 50% aqueous acetic acid (450 ml.) was heated on a steam-bath. Powdered iron (21 g., 0.36 mole) of 100 mesh was added in small portions at a rate which caused gentle boiling. Heating of the mixture was continued for one hour after the last portion of iron had been added. The mixture was then cooled slowly and diluted with 300 ml. of water. The addition of water completed the hydrolysis and precipitated the 8-amino-4,7-dichloroquinoline as the free base. The dirty brown solid thus obtained was placed in a Soxhlet extraction apparatus and the free base was extracted with 200 ml. of ether. Removal of the ether from the extract left 23.0 g. (88%) of light yellow needles which melted at 110–111°. The product showed the same melting point after crystallization from ethanol.

Anal. Calc'd for $C_9H_6Cl_2N_2$: C, 50.73; H, 2.84.
Found: C, 50.69; H, 3.09.

[5] All melting points are corrected. Microanalyses by Miss Theta Spoor and Miss Lillian Hruda.

Catalytic reduction of 8-amino-4,7-dichloroquinoline. Freshly-prepared palladium hydroxide on calcium carbonate (5.0 g.) was added to a solution of 8-amino-4,7-dichloroquinoline (1.0 g.) and potassium hydroxide (5.0 g.) in ethanol. The suspension was treated with hydrogen at half an atmosphere pressure until the expected quantity of hydrogen had been absorbed. After removal of the catalyst by filtration, the solvent was removed *in vacuo*. The residue was dissolved in ether and washed with water. Evaporation of the ether yielded a brown oil. This was treated with an aqueous methanol solution to give light yellow needles, m.p. 72–73.5°. A mixture of this compound with an authentic sample of 8-amino-7-chloroquinoline (2) showed the same melting point.

8-Amino-7-chloro-4-(4-diethylamino-1-methylbutyl)aminoquinoline (*VI*). A mixture of 8-amino-4,7-dichloroquinoline (30.0 g., 0.14 mole) and 4-amino-1-diethylaminopentane (120 g., 0.76 mole) was heated in an atmosphere of nitrogen at 180° for ten hours. The reaction mixture darkened only slightly under this treatment. The mixture was then taken up in ether (300 ml.) and washed successively with water (150 ml.), 5% sodium hydroxide (150 ml.), and water (150 ml.). After removal of the ether and the remaining 4-amino-1-diethylaminopentane *in vacuo*, the residue was distilled using a mercury-vapor diffusion pump. There was obtained 30.0 g. (64%) of a light yellow oil; b.p. 165–170° at 10^{-3} mm., n_D^{20} 1.6920.

Anal. Calc'd for $C_{18}H_{27}ClN_4$: C, 64.55; H, 8.12.
Found: C, 64.66; H, 8.23.

Treatment of a sample of the oil in ether with either anhydrous hydrogen chloride or syrupy phosphoric acid gave a white crystalline salt. However both of these salts were extremely hygroscopic, and they were not isolated. The *dipicrate* was readily prepared using alcohol as a solvent. Recrystallization from alcohol yielded bright yellow needles, m.p. 190–191°.

Anal. Calc'd for $C_{18}H_{27}ClN_4 \cdot 2C_6H_3N_3O_7$: C, 45.42; H, 4.16.
Found: C, 45.51; H, 4.25.

Treatment of 4,7-dichloro-8-nitroquinoline with 4-amino-1-diethylaminopentane. A mixture of 4,7-dichloro-8-nitroquinoline (20.0 g., 0.8 mole) and 4-amino-1-diethylaminopentane (35.0 g., 0.22 mole) was heated in an atmosphere of nitrogen. When the temperature reached 150°, a vigorous exothermic reaction occurred. Considerable decomposition resulted before the reaction subsided. The viscous mixture was treated with ether (300 ml.), and the ether extract was worked up in the usual manner. However only tarry material was obtained.

4-Chloro-6-methoxy-8-nitroquinoline.[6] 6-Methoxy-8-nitro-4-quinolinol (25.0 g., 0.11 mole) was heated with phosphorus pentachloride (25 g., 0.11 mole) and phosphorus oxychloride (60 ml.) at 130° for one hour. The phosphorus oxychloride was removed *in vacuo*, and the residue was decomposed with ice-water. The flocculent, white precipitate was removed by filtration and dried. There was obtained 22.0 g. (82%) of a white solid, m.p, 172–175°. Crystallization of the product from glacial acetic acid yielded white needles, m.p. 177–178° [lit. (4), 187–188°, but the nitrogen analysis reported differed from the theoretical by 0.86%].

Anal. Calc'd for $C_{10}H_7ClN_2O_3$: C, 50.33; H, 2.96.
Found: C, 50.13; H, 2.92.

8-Amino-4-chloro-6-methoxyquinoline. A mixture of 4-chloro-6-methoxy-8-nitroquinoline (22.0 g., 0.09 mole) and 50% aqueous acetic acid (320 ml.) was heated to boiling and 7 g. of powdered iron was added in small portions. The mixture was boiled for an hour, cooled, and diluted with two volumes of water. This caused hydrolysis with precipitation of the free base. The precipitate was collected, dried, and extracted with ether (200 ml.), using a Soxhlet extraction apparatus. The ether was removed from the extract, leaving 13.0 g. (68%) of grey needles, m.p. 90–94°. This product was recrystallized several

[6] We are indebted to John S. Meek for the preparation of this material.

times from alcohol and obtained almost white, m.p. 97–100°. The substance was analyzed as its *acetyl derivative* m.p. 206°, prepared in refluxing acetic anhydride.[7]

Anal. Calc'd for $C_{12}H_{11}ClNO_2$: C, 57.49; H, 4.42.

Found: C, 57.29; H, 4.67.

Hydrogenation of the nitro compound in ethanol over Adams' catalyst gave a reddish solid, m.p. 98–100°, which yielded the same *acetyl derivative*, m.p. and mixed m.p. 206°.

Treatment of 8-amino-6-methoxy-4-chloroquinoline with noval diamine. A solution of 8-amino-6-methoxy-4-chloroquinoline (12.0 g., 0.057 mole) in 4-amino-1-diethylaminopentane (50 g., 0.30 mole) was heated at 175° for ten hours in an atmosphere of nitrogen. The solution was then taken up in ether (200 ml.) and washed successively with water (100 ml.), 5% sodium hydroxide (100 ml.), and water (100 ml.). After removal of the ether and excess diamine *in vacuo*, the product was distilled under high vacuum. There was obtained 9.0 g. of a white solid; b.p. 125–135° (0.001 mm.), m.p. 90–94°. This was shown to be 8-amino-6-methoxy-4-chloroquinoline by the method of mixed melting points.

SUMMARY

The nitration of 4,7-dichloroquinoline has been shown to give 4,7-dichloro-8-nitroquinoline which has been converted into 8-amino-7-chloro-4-(4-diethylamino-1-methylbutyl)aminoquinoline. The preparation of the 6-methoxy analog was carried through to 8-amino-4-chloro-6-methoxyquinoline, but this substance failed to couple with 1-amino-4-diethylaminopentane under the conditions tried.

URBANA, ILL.

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[7] We are indebted to Robert E. Jones for the preparation of the acetyl derivative for analysis.

[Contribution from the Laboratory of Radiochemistry, University of Cincinnati]

COMPOUNDS FOR CANCER RESEARCH. IV. FURTHER BIFLUORYL AND BIFLUORYLIDENE DERIVATIVES[1]

ELIZABETH K. WEISBURGER, JOHN H. WEISBURGER, and FRANCIS EARL RAY

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Pinck's (1) recent hypothesis of the genesis of cancer attempts to explain the production of tumors by certain chemical agents according to the following mechanism. The carcinogenic compound, which must contain active hydrogens, is dehydrogenated *in vivo* to an ethylenic dimer. Cell substance, containing at least one active hydrogen, condenses with the ethylene so formed. Thus a chain of reactions is initiated which leads to the formation of a very large molecule of cell substance—potential cancer tissue.

Pinck concluded that the carcinogenic activity of 2-acetylaminofluorene (I) is due to the 2,2′-diacetylamino-9,9′-bifluorylidene (III) formed from I. Two reactions leading to the formation of the carcinogen were postulated.

A necessary, although not sufficient condition, if the hypothesis is to hold, is to establish the carcinogenic character of the compounds in question, both 2,2′-diacetylamino-9,9′-bifluoryl (II) and the bifluorylidene, III.

This hypothesis may explain the mode of action of 2-acetylaminofluorene in causing cancer but gives no explanation for the production of tumors in organs distant from the site of application. Possibly, when the 2-acetylaminofluorene enters the body, part is hydrolyzed to 2-aminofluorene which is solubilized by the purines present in the blood stream (2). It can thus be carried about the body to various organs where tumors form because of the reaction postulated by Pinck.

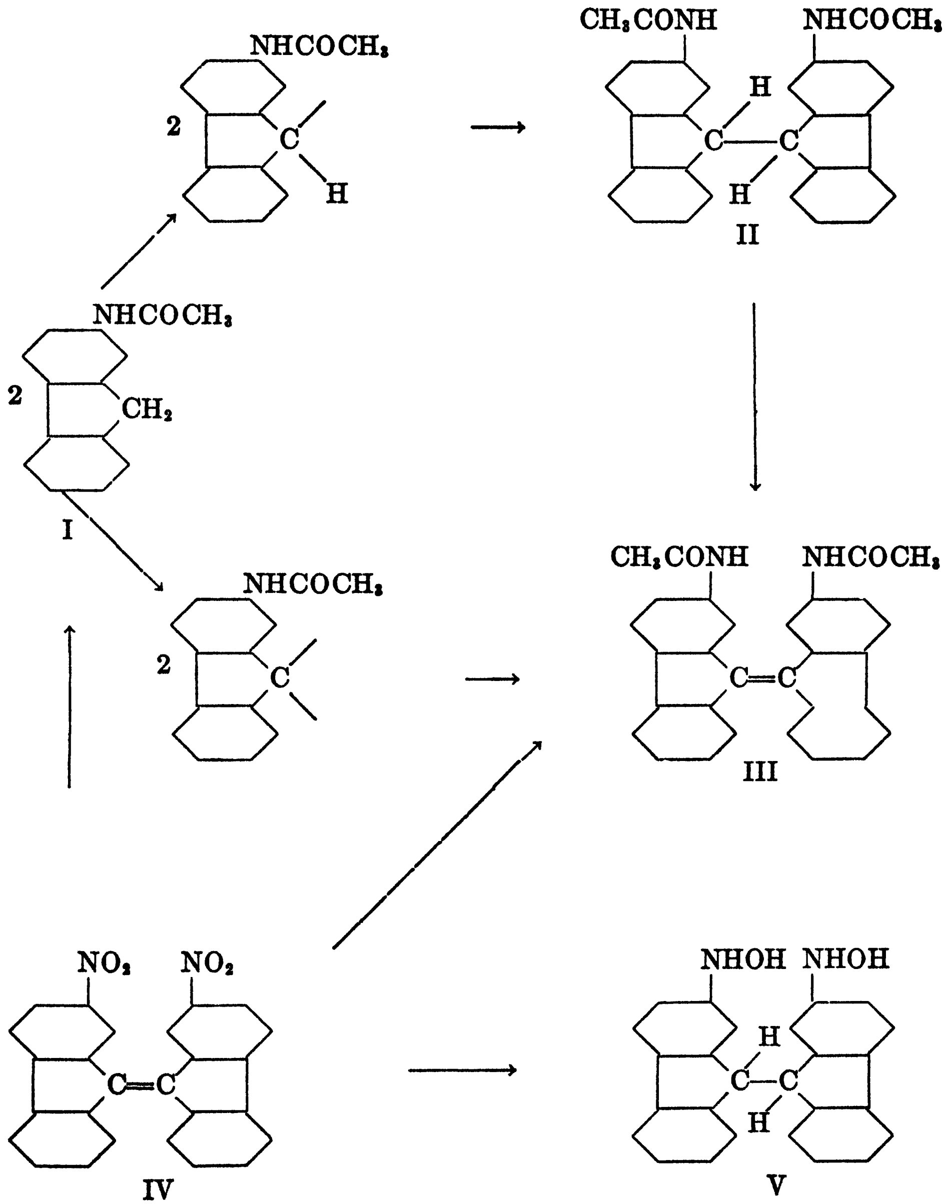
In order to obtain experimental evidence concerning Pinck's hypothesis 2,2′-diacetylamino-9,9′-bifluoryl and bifluorylidene were prepared. It has been shown that 2-nitro-9-iodofluorene does not spontaneously lose iodine with formation of 2,2′-dinitro-9,9′-bifluoryl (3). However, the corresponding bifluorylidene derivative was readily prepared by dehydrohalogenation of 2-nitro-9-bromofluorene with potassium hydroxide in methanol-acetone solution according to the method of Thiele and Wanscheidt (4).

The dinitro derivative, IV, was reduced to the intermediate 2,2′-dihydroxylamino-9,9′-bifluoryl (V), with zinc and calcium chloride in an ethanol-dioxane solution. Reduction of either IV or V by zinc dust and acetic acid yielded 2,2′-diacetylamino-9,9′-bifluoryl (II). No attempt was made to separate or identify any *meso* or *racemic* forms.

The authors observed on previous occasions that at the melting point a bifluoryl compound loses hydrogen with conversion to the unsaturated bifluorylidene (5). This fact was used to prepare 2,2′-diacetylamino-9,9′-bifluorylidene (III). The bifluoryl derivative, II, was dissolved in refluxing biphenyl, whereby

[1] This investigation was supported by research grant C 341 from the National Cancer Institute of the U. S. Public Health Service.

it was dehydrogenated. After cooling, the biphenyl was removed by extraction with petroleum ether, leaving a mixture of bifluorylidene and unchanged bifluoryl. Attempts to dehydrogenate the bifluoryl by mild oxidizing agents



such as ferric chloride or hydrogen peroxide were not successful. However, it was found that III could be obtained directly by reduction of IV with iron and glacial acetic acid. The double bond was not reduced under these conditions.

The difference in the melting points of the 2,2′-diacetylamino-9,9′-bifluorylidene obtained by the two methods may have been due to *cis* and *trans* isomers.

The diacetylaminobifluorylidenes were all converted to the bifluoryl by action of zinc and glacial acetic acid.

EXPERIMENTAL

9-Bromo-2-nitrofluorene. This compound was prepared according to the method of Korczynski, *et al.* (6).

2,2′-Dinitro-9,9′-bifluorylidene (IV). Fifty-six grams of 9-bromo-2-nitrofluorene was dissolved in 400 cc. of acetone and the solution cooled to room temperature. Eleven grams of potassium hydroxide in 100 cc. of methanol and 50 cc. of acetone were added slowly with stirring. The orange-red precipitate which began forming immediately was allowed to settle, filtered off, washed and dried. It weighed 44 g. The melting point was over 360° as reported by Korczynski (6).

2,2′-Dihydroxylamino-9,9′-bifluoryl (V). Thirty grams of 2,2′-dinitro-9,9′-bifluorylidene was suspended in 500 cc. of ethanol and 200 cc. of dioxane containing 10 g. of calcium chloride in 75 cc. of water. Eighty grams of zinc dust was added, and the whole thoroughly mixed and refluxed for 2 hours. The excess zinc was filtered off and the filtrate diluted with 2 l. of water. The tan-yellow precipitate weighed 22 g. It reduced Fehling's solution and reddened on the copper block but did not melt below 360°. It could be recrystallized from benzene or xylene.

Anal. Calc'd for $C_{26}H_{20}N_2O_2$: N, 7.14; Mol. wt. 392.
Found: N, 7.31; Mol. wt. 383.

2,2′-Diacetylamino-9,9′bifluoryl (II). A. By reduction of IV. One gram of 2,2′-dinitro-9,9′-bifluorylidene was refluxed with 4 g. of zinc dust in 50 cc. of glacial acetic acid for 2¾ hours. Then 2 cc. of acetic anhydride was added and the mixture refluxed for 15 minutes. After filtration and dilution of the filtrate with water a white precipitate formed. This after drying weighed 0.9 g. and melted at 255° (block). After recrystallization from dioxane or acetic acid it melted at 328° (block).

Anal. Calc'd for $C_{30}H_{24}N_2O_2$: N, 6.30. Found: N, 6.06.

B. By reduction of V. Thirty grams of the hydroxylamino compound was dissolved in 400 cc. of glacial acetic acid and 40 g. of zinc dust added in portions over a period of one hour. Then 40 cc. of acetic anhydride was added dropwise. After filtration and dilution of the filtrate to 2 l. with water, 34 g. of crude 2,2′-diacetylamino-9,9′-bifluoryl was obtained, m.p. 255°.

2,2′-Diacetylamino-9,9′-bifluorylidene (III). A. By fusion of II. A mixture of 14 g. of 2,2′-diacetylamino-9,9′-bifluoryl and 60 g. of biphenyl was heated in a metal bath for 15 minutes at a temperature sufficient to keep the biphenyl refluxing. The red mixture which formed was extracted in a Soxhlet with petroleum ether for two hours to remove the biphenyl. The red residue weighed 14 g. Of this amount 2 g. was soluble in benzene and the fine carmine-red crystals melted at 190° after recrystallization from benzene.

Anal. Calc'd for $C_{30}H_{22}N_2O_2$: N, 6.33. Found: N, 6.27.

The material insoluble in benzene yielded the unchanged bifluoryl after two recrystallizations from glacial acetic acid using charcoal. A trace of the higher-melting isomer (see B below) was also obtained.

B. By reduction of IV. One gram of IV was refluxed with 4 g. of iron powder and 40 cc. of glacial acetic acid for 1½ hours. After adding 1 cc. of concentrated hydrochloric acid and boiling for one minute the mixture was filtered. The solution was refluxed with 5 cc. of acetic anhydride for 15 minutes, diluted to 250 cc. with water, and acidified with 10 cc. of concentrated hydrochloric acid to dissolve basic iron salts. The precipitate weighed 1.2 g., and melted at 240°. After recrystallizing from glacial acetic acid the dark red microcrystals melted at 264–265°.

Anal. Calc'd for $C_{30}H_{22}N_2O_2$: N, 6.33; Mol. wt. 442. Found: N, 6.05; Mol. wt. 433.

It appeared probable that some of the lower-melting isomer (see A above) was present in the crude material and mother liquors but it was not obtained in a pure state.

SUMMARY

In order to obtain experimental evidence of Pinck's hypothesis of the genesis of cancer, the synthesis of the possible carcinogens, 2,2'-diacetylamino-9,9'-bifluoryl and 2,2'-diacetylamino-9,9'-bifluorylidene, has been accomplished.

The carcinogenetic properties of these compounds are being investigated by Dr. H. P. Morris of the National Cancer Institute and will be reported by him subsequently.

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY, RADIUM INSTITUTE, UNIVERSITY OF PARIS]

CARCINOGENIC DERIVATIVES OF CARBAZOLE. I. THE SYNTHESIS OF 1,2,7,8-, 1,2,5,6-, AND 3,4,5,6-DIBENZOCARBAZOLE AND SOME OF THEIR DERIVATIVES[1]

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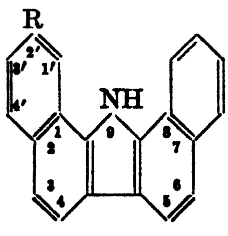
1,2,7,8-, (I, R = H), 1,2,5,6-, (II, R = H), and 3,4,5,6-dibenzocarbazole (III) play an important role in the chemistry of cancer, both on account of their activity in promoting malignant growths in various organs (1) and of their presumed endogenous formation from certain carcinogenic azo compounds of the naphthalene series (2).



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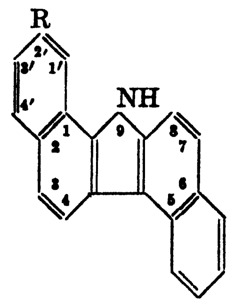

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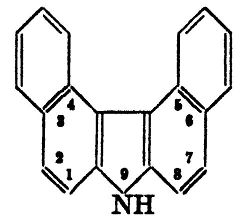

III

1,2,5,6-Dibenzocarbazole has also been found to possess considerable inhibitory powers against the growth of Walker rat carcinoma (3). This provided an incentive to the study of the relationship between substitution and carcinogenicity or growth-inhibitory powers in this series, and general methods for the synthesis of bis-angular dibenzocarbazoles have therefore been more thoroughly investigated.

The procedure most commonly used hitherto for preparing these three dibenzocarbazoles is based upon the Bucherer reaction. This consists in the heating of sodium bisulfite and α- or β-naphthylhydrazine, alone in the case of 1,2,7,8- and 3,4,5,6-dibenzocarbazole, or with 3-hydroxy-2-naphthoic acid in the case of 1,2,5,6- and 3,4,5,6-dibenzocarbazole (4). However, because of the relative inaccessibility of substituted naphthylhydrazines, this method is hardly feasible for the synthesis of functional derivatives and homologs of dibenzocarbazoles.

The deamination by mineral acids of *o,o'*-diamines obtained in the benzidine rearrangement of hydrazonaphthalenes has been used for the preparation of 1,2,7,8-dibenzocarbazole by Nietzski and Goll (5), of 3,4,5,6-dibenzocarbazole by Meisenheimer and Witte (6), and, more recently, of 1,2,5,6-dibenzocarbazole

[1] The work described in this paper was carried out with the financial support of the U. S. Public Health Service, Federal Security Agency.

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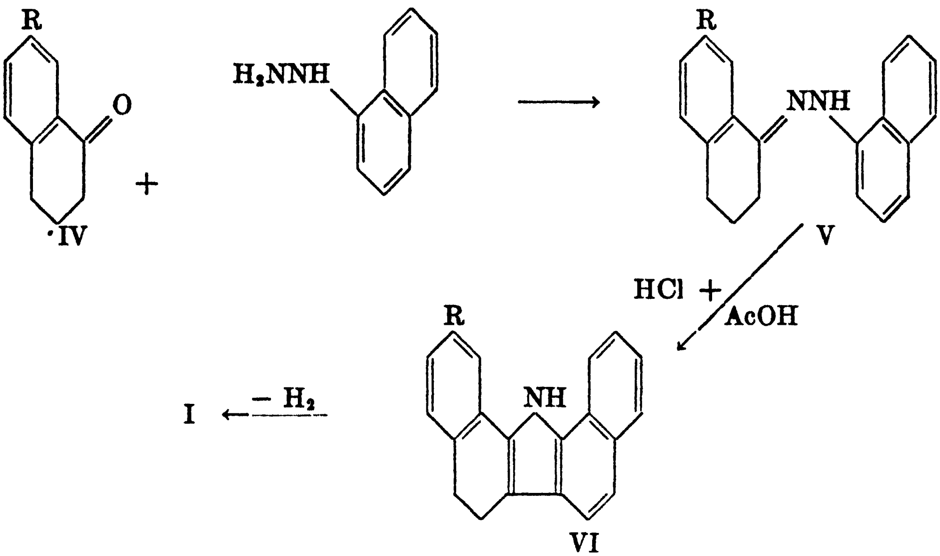
by Warren (7). An extension of this procedure to the preparation of substituted dibenzocarbazoles is also precluded by reason of the inaccessibility of *o,o'*-diamines with ascertained constitution, in the naphthalene series.

The Japp-Maitland procedure (8) which involves the heating at high temperature of naphthols with naphthylhydrazines and naphthylhydrazine hydrochlorides gives extremely low yields, since naphthylhydrazines and their salts are highly sensitive to heat.

We have now found that the Fischer-Borsche synthesis of indoles and carbazoles (9), when applied to naphthylhydrazines and tetralones, permitted the easy preparation of the three bis-angular dibenzocarbazoles and of a series of their homologs and functional derivatives.

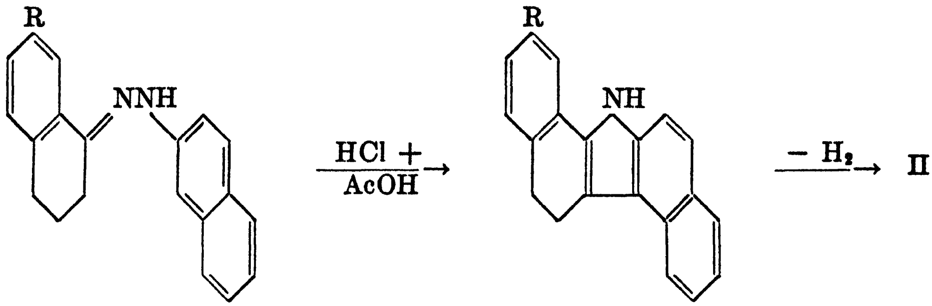
1,2,7,8-Dibenzocarbazole series. Under the influence of a solution of dry hydrochloric acid in glacial acetic acid, tetralone-1-α-naphthylhydrazone (V, R = H) readily underwent cyclization into 3,4-dihydro-1,2,7,8-dibenzocarbazole



(VI, R = H); this was easily dehydrogenated into 1,2,7,8-dibenzocarbazole (I) by means of chloranil, a reagent recommended by Barclay and Campbell (10) for the dehydrogenation of tetrahydrocarbazoles, after Arnold, *et al.* (11) had used it with success for the preparation of various aromatic hydrocarbons.

The replacement of tetralone-1 in the above synthesis by 7-nitrotetralone-1 (IV, R = NO_2, obtained as the main product in the nitration of tetralone-1), yielded 2'-nitro-1,2,7,8-dibenzocarbazole (I, R = NO_2) *via* 2'-nitro-3,4-dihydro-1,2,7,8,-dibenzocarbazole (VI, R = NO_2), which underwent spontaneous dehydrogenation on being heated above its melting point. 7-Methoxytetralone-1 (IV, R = OCH_3, conveniently prepared from anisole by means of the routine succinic anhydride procedure) gave similarly 2'-methoxy-1,2,7,8-dibenzocarbazole (I, R = OCH_3) *via* the corresponding 3,4-dihydro derivative (VI, R = OCH_3).

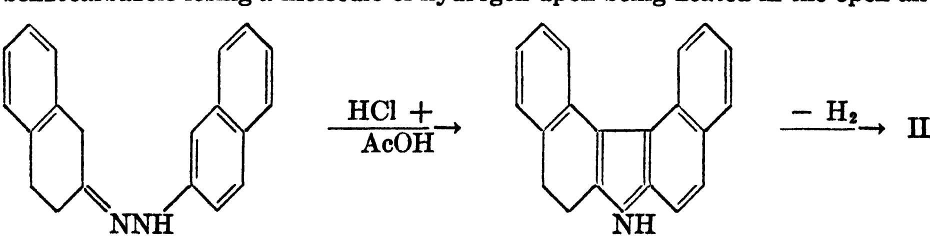
1,2,5,6-Dibenzocarbazole series. Owing to the outstanding physiological properties of 1,2,5,6-dibenzocarbazole, many more compounds in this group have been prepared. The syntheses which involved β-naphthylhydrazone followed a similar pattern as for the preceding series, tetralone-1 β-naphthylhydrazone (VII, R = H) being cyclized into 3,4-dihydro-1,2,5,6-dibenzo-



VII VIII

carbazole (VIII, R = H), and the latter dehydrogenated with chloranil. In the preparation of 2′-nitro-1,2,5,6-dibenzocarbazole (II, R = NO_2) from 7-nitrotetralone-1 β-naphthylhydrazone (VII, R = NO_2), the intermediary dihydro compound (VIII, R = NO_2) lost a molecule of hydrogen so easily that it could not be isolated. 7-Methyltetralone-1 (IV, R = CH_3) and 7-*ter*-butyltetralone-1 (IV, R = *ter*-C_4H_9), prepared from toluene and *ter*-butylbenzene by the succinic anhydride method, gave respectively 2-methyl-, (II, R = CH_3) and 2′-*ter*-butyl-1,2,5,6-dibenzocarbazole (II, R = *ter*-C_4H_9) *via* the stable corresponding 3,4-dihydro derivatives. From 7-methoxytetralone-1,2′-methoxy-1,2,-5,6-dibenzocarbazole (II, R = OCH_3) was similarly obtained *via* 2′-methoxy-3,4-dihydro-1,2,5,6-dibenzocarbazole (VIII, R = OCH_3).

3,4,5,6-Dibenzocarbazole. This compound was readily prepared from tetralone-2 β-naphthylhydrazone, the intermediary 1,2-dihydro-3,4,5,6-dibenzocarbazole losing a molecule of hydrogen upon being heated in the open air:



As homologs of tetralone-2 have now become readily accessible through the Cornforth-Robinson reduction of β-methoxynaphthalenes (12), this procedure makes possible the synthesis of homologs of 3,4,5,6-dibenzocarbazole, and this work is being continued.

Most of the new substances quoted above are now under biological investigation by Professor Lacassagne for potential carcinogenic and growth-inhibitory properties.

EXPERIMENTAL[3]

Preparation of intermediates. α- and β-*Naphthylhydrazine hydrochlorides* used in these experiments were prepared by reduction of α- and β-naphthyldiazonium chlorides with stannous chloride, according to the literature (yield 80–85%).

Tetralone-1 was conveniently obtained in 95% yield from γ-phenylbutyryl chloride by cyclization with aluminum chloride in benzene medium at 0°, and this procedure was found superior to the catalyzed air-oxidation of tetralin.

7-Methyltetralone-1 (13) was similarly prepared in 90% yield by cyclization of γ-*p*-tolylbutyric chloride; the intermediary γ-*p*-tolylbutyric acid was obtained either by Clemmensen reduction of γ-*p*-toluoylpropionic acid, according to Martin (14), or better, in large scale preparations and with 40% over-all yield, by a malonic ester synthesis starting from β-*p*-tolylethanol *via* β-*p*-tolylethyl bromide.

7-ter-Butyltetralone-1 was obtained from *ter*-butylbenzene according to Buu-Hoï and Cagniant (15).

7-Methoxytetralone-1 (16) was prepared by cyclization of γ-*p*-anisylbutyryl chloride, also in benzene solution at −5° to 0°. In this case too, the malonic ester synthesis of γ-*p*-anisylbutyric acid, starting from β-*p*-anisylethyl bromide, is preferable in large scale operations to the Clemmensen-Martin reduction of γ-*p*-anisoylpropionic acid (14).

7-Nitrotetralone-1 was obtained in excellent yield by nitration of tetralone-1 with fuming nitric acid (d = 1.49), according to von Braun's procedure (17).

Tetralone-2 was prepared from neroline as indicated in the literature (18); a considerable dropping off in the yield was noticeable when more than 25 to 30 g. of neroline was reduced at a time. It may be mentioned that the blue-colored substance which arises when tetralone-2 comes into contact with alkaline reagents is probably an indigoid dye resulting from the oxydative duplication of the molecule.

The *reagent* for the cyclization of the hydrazones was made by saturating pure acetic acid with dry hydrochloric acid.

3,4-Dihydro-1,2,7,8-dibenzocarbazole (VI; R = H). A mixture of 2.6 g. of tetralone-1, 4 g. of α-naphthylhydrazine hydrochloride, and 3 g. of sodium acetate, was refluxed with 50 ml. of ethanol for two hours. After cooling, an excess of water was added; the precipitate of the crude naphthylhydrazone was collected by suction, washed with water, and dissolved in 20 ml. of the cyclization reagent. After five minutes of heating on a water-bath, the mixture was poured into water, and the precipitate was washed thoroughly with water, dried, and crystallized from mixture of benzene and ligroïn. Almost colorless prisms melting at 178°, easily soluble in benzene, and giving a dark brown coloration with an alcoholic solution of picric acid were obtained. The yield was 2.5 g.

Anal. Calc'd for $C_{20}H_{15}N$: N, 5.2. Found: N, 5.3.

1,2,7,8-Dibenzocarbazole. A mixture of 1.2 g. of the foregoing dihydro compound, 1.7 g. of chloranil, and 30 ml. of dry xylene was refluxed for two hours. After cooling, the tetrachlorohydroquinone was filtered off by suction and washed with some ml. of xylene; the filtrate was shaken with a 10% aqueous solution of sodium hydroxide and then with water, and dried over calcium chloride. After the evaporation of xylene in a vacuum, the residue obtained was recrystallized twice from benzene, giving pale yellowish needles (1 g.) melting at 212°, and dissolving in sulfuric acid with a brown-red halochromic coloration. Nietzski and Goll (5) report the melting point as 216°.

2'-Nitro-3,4-dihydro-1,2,7,8-dibenzocarbazole (VI; R = NO_2). Reaction between 3.5 g. of 7-nitrotetralone-1, 5.5 g. of α-naphthylhydrazine hydrochloride, and 4.2 g. of sodium acetate in 50 ml. of alcohol gave a crude naphthylhydrazone which was cyclized as in the preceding case. Crystallization from xylene of the substance thus obtained gave fine, bright red needles melting at 270°. The yield was 2 g. Prolonged heating above the melting point transformed this substance into the following one.

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[3] All melting points are uncorrected, and were taken with a Maquenne-block.

Anal. Calc'd for $C_{20}H_{14}N_2O_2$: N, 8.9. Found: N, 8.6.

2'-Nitro-1,2,7,8-dibenzocarbazole (I; R = NO_2). Dehydrogenation of 1.7 g. of the preceding compound with 1.5 g. of chloranil in 40 ml. of xylene for two hours, followed by the usual treatment, gave a substance (1.5 g.) which crystallized from xylene in fine, shiny, deep red needles melting at 358°, almost insoluble in alcohol, easily soluble in pyridine.

Anal. Calc'd for $C_{20}H_{12}N_2O_2$: N, 8.9. Found: N, 8.6.

2'-Methoxy-3,4-dihydro-1,2,7,8-dibenzocarbazole (VI; R = OCH_3). This substance was obtained with a yield of 3 g. from 3 g. of 7-methoxytetralone-1, 5 g. of α-naphthylhydrazine hydrochloride, and 3 g. of sodium acetate, following the usual procedure. It crystallized from ligroïn in fine, pale yellowish needles melting at 173–174°, very soluble in benzene.

Anal. Calc'd for $C_{21}H_{17}NO$: N, 4.7. Found: N, 4.6.

2'-Methoxy-1,2,7,8-dibenzocarbazole (I; R = OCH_3). Dehydrogenation of 2 g. of the dihydro compound with 3 g. of chloranil in 40 ml. of xylene for two hours gave 1.5 g. of a substance separating from benzene in pale yellowish needles melting at 187°, giving a brown-red coloration with sulfuric acid.

Anal. Calc'd for $C_{21}H_{15}NO$: N, 4.7. Found: N, 4.7.

3,4-Dihydro-1,2,5,6-dibenzocarbazole (VIII; R = H). Two and six-tenths g. of tetralone-1, treated with 4 g. of β-naphthylhydrazine and 3 g. of sodium acetate, gave a naphthylhydrazone which was cyclized as usual; the compound obtained (2.5 g.) crystallized from benzene in almost colorless prisms melting at 197°.

Anal. Calc'd for $C_{20}H_{15}N$: N, 5.2. Found: N, 5.0.

1,2,5,6-Dibenzocarbazole. One and one-tenth g. of the foregoing compound treated with 1.5 g. of chloranil gave an almost quantitative yield of the dehydrogenated product, which crystallized from benzene in pale yellowish needles melting at 237–238°. The literature (4, 8) indicates 231° as the melting point.

2'-Nitro-1,2,5,6-dibenzocarbazole (II; R = NO_2). A mixture of 3.5 g. of 7-nitrotetralone-1, 5.5 g. of β-naphthylhydrazine hydrochloride, and 4.2 g. of sodium acetate was refluxed for two hours with 100 ml. of ethanol. After cyclization of the naphthylhydrazone in the usual way, a red substance was obtained, which was practically insoluble in the ordinary solvents. After crystallization from nitrobenzene, shiny deep red prisms were obtained, which melted at 365°; the yield was 3.5 g. This substance was recovered unchanged after treatment with chloranil.

Anal. Calc'd for $C_{20}H_{12}N_2O_2$: N, 8.9. Found: N, 8.7.

2'-Methyl-3,4-dihydro-1,2,5,6-dibenzocarbazole (VIII; R = CH_3). This substance was obtained with a yield of 5 g. from 3.2 g. of 7-methyltetralone-1, 5 g. of β-naphthylhydrazine, and 4.5 g. of sodium acetate. It separated from benzene in pale yellowish microcrystalline prisms melting at 228°, and giving a dark brown complex with picric acid.

Anal. Calc'd for $C_{21}H_{17}N$: N, 5.2. Found: N, 5.0.

2'-Methyl-1,2,5,6-dibenzocarbazole (II; R = CH_3). Dehydrogenation of 5 g. of the preceding substance with 7 g. of chloranil in 50 ml. of xylene gave an almost quantitative yield of a compound separating from xylene in pale yellowish microcrystalline prisms melting at 285–286°.

Anal. Calc'd for $C_{21}H_{15}N$: N, 5.2. Found: N, 4.9.

2'-ter-Butyl-3,4-dihydro-1,2,5,6-dibenzocarbazole. From 1.5 g. of 7-*ter*-butyltetralone-1, 3 g. of β-naphthylhydrazine hydrochloride, and 2.6 g. of sodium acetate, a hydrazone was obtained which, on cyclization, gave a substance crystallizing from ligroïn in almost colorless needles melting at 169–170° and giving a dark brown complex with picric acid. The yield was 1 g.

Anal. Calc'd for $C_{24}H_{23}N$: N, 4.3. Found: N, 4.0.

2'-ter-Butyl-1,2,5,6-dibenzocarbazole. This substance, obtained from 1 g. of the preceding dihydro compound and 1.5 g. of chloranil with an almost quantitative yield, crystallized from benzene in pale yellowish needles melting at 226°.

Anal. Calc'd for $C_{24}H_{19}N$: N, 4.3. Found: N, 4.0.

2'-Methoxy-3,4-dihydro-1,2,5,6-dibenzocarbazole. Three grams of 7-methoxytetralone-1,

5 g. of β-naphthylhydrazine hydrochloride, and 3 g. of sodium acetate, yielded 4.5 g. of this substance, which separated from benzene in microcrystalline yellowish prisms melting at 200°.

Anal. Calc'd for $C_{21}H_{17}NO$: N, 4.7. Found: N, 4.5.

2'-Methoxy-1,2,5,6-dibenzocarbazole (II; R = OCH_3). Four and one-half g. of the foregoing compound, treated with 5 g. of chloranil, gave 4 g. of the dehydrogenated product, which crystallized from xylene in fine yellowish prisms melting at 258°. Brown-red coloration with sulfuric acid.

Anal. Calc'd for $C_{21}H_{15}NO$: N, 4.7. Found: N, 4.5.

3,4,5,6-Dibenzocarbazole (III). A mixture of 1.5 g. of tetralone-2, 2.5 g. of β-naphthylhydrazine hydrochloride, and 2 g. of sodium acetate was refluxed in 40 ml. of ethanol for one hour, and the crude naphthylhydrazone indolized as usual. The cyclization product (1 g.) was either distilled or heated with chloranil (1.4 g.) in xylene solution for one hour, and the mixture worked up as usual. One gram of 3,4,5,6-dibenzocarbazole was obtained, which crystallized from a mixture of benzene and ligroïn in fine yellowish prisms melting at 154°. The literature (4, 8) gives 155°.

SUMMARY

1. A convenient method is described for the preparation of the three carcinogenic bis-angular dibenzocarbazoles.

2. The synthesis is reported of a number of functional derivatives and homologs of 1,2,7,8- and 1,2,5,6,-dibenzocarbazole, desired for biological experimentation.

PARIS (V), FRANCE

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[CONTRIBUTION FROM THE WEIZMANN INSTITUTE OF SCIENCE]

INVESTIGATIONS IN THE DDT SERIES

L. HASKELBERG AND D. LAVIE

Received January 31, 1949

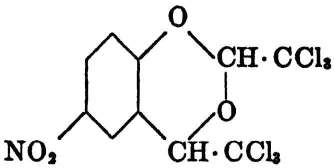
In a previous paper (1) the condensation of fluorene with chloral was described, but the position in which the condensation took place had not been elucidated. We have now found that dehydrohalogenation of the 1,1-difluorenyl-2,2,2-trichloroethane and subsequent oxidation with chromic acid leads to a difluoroenyl ketone which has the melting point (297–298°) given in the literature (2) for the 2,2′-compound. In accordance with the well-known rules for the substitution in the fluorene nucleus (3), the condensation with chloral appears to take place in the 2- position.

In our previous publication, the reaction of chloral with 2-nitrophenol has been described. We have reinvestigated the condensation of chloral with the *p*-isomer under the influence of fuming sulfuric acid. Chattaway (4) has isolated substance (I) from this reaction, in which 1 mole of the phenol has condensed with 2 moles of chloral. We have found that under the conditions employed in our experiments the yield of (I) is only 2.5%, whilst a yield of 15% was obtained of a second substance melting at 179° which, in contradistinction to (I), is soluble in alkali. It is undoubtedly the expected substance of formula (II), as indicated by the fact that methanolic alkali splits off 1 mole of hydrochloric acid, giving in 61% yield a substance of m.p. 225–226° which according to the analyses is the corresponding ethylene (III).

We have extended our investigation to the condensation of chloral hydrate with benzonitrile. Under the influence of sulfuric acid a yield of 60%, under the influence of chlorosulfonic acid a yield of 85%, was obtained of a substance melting at 271° and corresponding to the formula $C_{16}H_{13}Cl_3N_2O_2$. To this substance Hepp and Spiess (5) have ascribed formula (IV), whilst Martin and Wain (6) assumed (with some reservation) that normal condensation has taken place, accompanied by hydrolysis of the cyano to amide groups (V). The hydrolysis of the substance with either sulfuric acid in glacial acetic acid or with aqueous alkali gives benzoic acid, however, and equally the treatment with methanolic sodium hydroxide gives benzamide. Formula (IV) appears, therefore, to represent the structure of the substance. In order to verify this conclusion, we have prepared the amide (V) by an unambiguous method: by condensation of toluene with chloral, according to Fischer (7), we have obtained in 53% yield the 1,1-di(*p*-tolyl)-2,2,2-trichloroethane, which was oxidized by means of sodium dichromate and concentrated sulfuric acid to the corresponding dicarboxylic acid (VI), m.p. 271–272°. This was converted *via* the dichloride into the diamide of m.p. 227°. This substance which had definitely formula (V), was not identical with the condensation product of benzonitrile and chloral hydrate.

As benzamide does not react with chloral under the conditions employed for

benzonitrile, one has to conclude that the observed hydrolysis of the cyano group does not take place before the condensation, but follows it.



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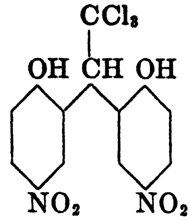

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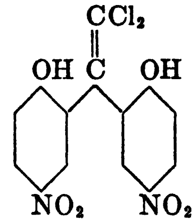

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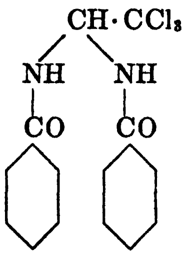

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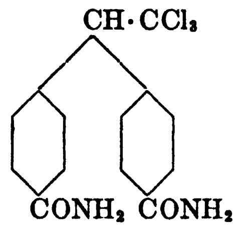

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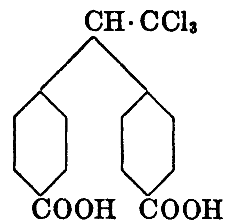
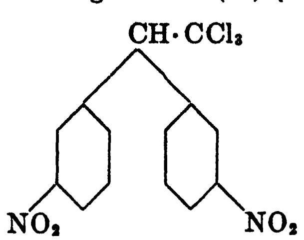


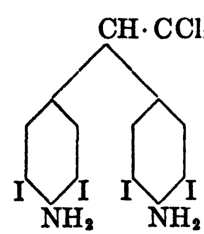
VI

In our previous communication it was shown that 1,1-diphenyl-2,2,2-trichloroethane is nitrated mainly in the two *p*-positions. Investigation of the mother liquors has led to the isolation of a second isomer of m.p. 118°. This contains the nitro groups in the *m*-positions to the side chain (VII): dehydrohalogenation led to a 1,1-dinitrophenyl-2,2-dichloroethylene of m.p. 128–129° which could be oxidized to 3,3′-dinitrobenzophenone of m.p. 160°, identical with that described by Staedel (8).

In view of the interest which the previously described 1,1-di-(4′-aminophenyl)-2,2,2-trichloroethane exhibits as tuberculostatic agent, several derivatives were prepared. Treatment with iodine monochloride in glacial acetic acid gave a tetraiodo derivative of m.p. 145° (dec.) which by analogy (9) should be ascribed the following formula (10) (VIII).



VII



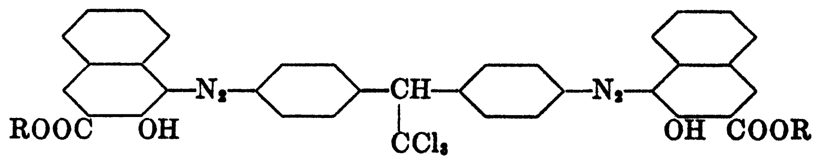
VIII

Also the bis(trichloroacetyl) derivative of m.p. 199° was prepared in which the lipophilic character should be enhanced in comparison with the parent substance (11). It forms a molecular compound with 1 mole of benzene

Furthermore, we have used the diamino compound for the preparation of some

azo dyes. After diazotization of both amino groups, it was coupled with 2-hydroxynaphthalene-3-carboxylic acid, its methyl ester, and its anilide, respectively. All three dye-stuffs (IX) were obtained in pure form, while those with α- and β-naphthylamine could not be purified completely.

Attention is drawn to the fact that in the meantime the same diamino compound has been described by Balaban and Levy (12).[1]



R=H
=CH_3
=C_6H_5NH

IX

EXPERIMENTAL

Di-(2-fluorenyl) ketone. Just 0.5 g. of the previously described 1,1-difluorenyl-2,2-dichloroethylene was oxidized with 1.5 g. of chromic acid in 10 cc. of glacial acetic acid at the boiling temperature. The green reaction mixture was diluted with water and the solid product which separated was recrystallized from glacial acetic acid. The lemon-yellow crystals melted at 297–298° as indicated by Dziewonsky and Panek (2) and gave the correct analytical figures.

Anal. Calc'd for $C_{27}H_{14}O_2$: C, 83.9; H, 3.6.
Found: C, 83.9; H, 4.2.

Condensation of chloral hydrate and p-nitrophenol. To a mixture of 20 g. of *p*-nitrophenol, 15 g. of concentrated and 15 g. of fuming sulfuric acid, 11 g. of chloral hydrate, diluted with 10 g. of concentrated and 10 g. of fuming sulfuric acid, was added slowly with vigorous stirring. The stirring was continued for 8 hours without cooling and the product was poured onto crushed ice. It was then filtered, washed with warm water and triturated at 50° with 100 cc. of an aqueous 10% sodium hydroxide solution.

The *filtrate* was decolorized with active carbon and acidified with dilute hydrochloric acid. Four and three-tenths g. of *1,1-(2'-hydroxy-5'-nitrophenyl)-2,2,2-trichloroethane* (II) separated and were recrystallized from toluene and glacial acetic acid; colorless prisms of m.p. 179°, yield, 15%.

Anal. Calc'd for $C_{14}H_9Cl_3N_2O_6$: C, 41.2; H, 2.2; N, 6.8.
Found: C, 41.5; H, 2.8; N, 6.4.

From dilute alcohol or dilute acetic acid, the substance crystallizes with 1 mole of water. The *hydrate* melts with gas evolution at 146°, solidifies again, and melts finally at 179°.

Anal. Calc'd for $C_{14}H_9Cl_3N_2O_6 \cdot H_2O$: H_2O, 4.2. Found: H_2O, 4.6.

The *alkali-insoluble* part (1.5 g.) was recrystallized from glacial acetic acid or alcohol; it melted at 144–145°; yield 2.5%. It was identical with the heterocyclic compound (I) described by Chattaway (4).

Anal. Calc'd for $C_{10}H_5Cl_6NO_4$: C, 28.8; H, 1.2.
Found: C, 29.1; H, 1.4.

1,1-(2'-Hydroxy-5'-nitrophenyl)-2,2-dichloroethylene. (III) The preceding substance

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[1] In our previous communication (1), the assumption had been made that the product of m.p. 239–246° (dec.) described by Burger, Graf, and Bailey [*J. Am. Chem. Soc.*, **68**, 1725 (1946)] was the diacetyl derivative of the above di-*p*-amino compound which we had obtained. Dr. Burger has kindly informed us that this has been confirmed by determination of the mixed m.p. of the two respective samples.

(2 g.) was refluxed for 12 hours with a solution of 0.8 g. of sodium hydroxide in 10 cc. of methanol. A red precipitate was formed which was isolated by filtration, dissolved in water and acidified with dilute hydrochloric acid. Recrystallized from 60% alcohol or 50% acetic acid, m.p. 225–226°, yield, 61.%.

Anal. Calc'd for $C_{14}H_8Cl_2N_2O_6$: C, 45.3; H, 2.1; N, 7.5.
Found: C, 45.1; H, 2.5; N, 7.9.

Condensation of chloral hydrate with benzonitrile. (*a*) To a cold mixture of 16 g. of chloral hydrate, 25 g. of concentrated and 25 g. of fuming sulfuric acid, 20 g. of benzonitrile was added with vigorous stirring. The addition caused only a slight rise in temperature. After one hour, the mixture was diluted with ice and the product filtered, washed and recrystallized from glacial acetic acid; long, soft needles of m.p. 271° (dec.), yield 60%.

(*b*) To a solution of 3.2 g. of chloral hydrate in 15 cc. of carbon tetrachloride, was added with stirring at 20°, 2.3 g. of chlorosulfonic acid. After 10 minutes, 4.1 g. of benzonitrile was added, followed by another 2.5 g. of chlorosulfonic acid. The exothermic reaction was checked by external cooling, and the product, after an hour, treated as above, yield 85%. The analysis and the following hydrolysis experiments show that the substance is the *N,N-dibenzoyl derivative* of 1,1-diamino-2,2,2-trichloroethane (IV).

Anal. Calc'd for $C_{16}H_{13}Cl_3N_2O_2$: C, 51.6; H, 3.5; N, 7.5.
Found: C, 51.6; H, 3.5; N, 7.7.

Hydrolysis. (*a*) A mixture of 2 g. of IV, 2 cc. of 50% sulfuric acid and 3 cc. of glacial acetic acid was refluxed for 3 hours. The reaction product was precipitated by addition of water and identified as *benzoic acid.*

(*b*) A mixture of 1 g. of IV and 10 cc. of a 10% aqueous sodium hydroxide solution was refluxed for 5 hours. The product was pure *benzoic acid.*

(*c*) A mixture of 3.7 g. of IV, 0.5 g. of sodium hydroxide and 50 cc. of methyl alcohol was refluxed for 5 hours. The solvent was removed and the residue dried on a porous plate and recrystallized from butyl alcohol. The crystals (1 g.) melted at 128° and were identified as *benzamide.*

Condensation of chloral hydrate with toluene. According to Fischer (7), 600 g. of concentrated sulfuric acid was added, at ice temperature and with violent agitation, to a mixture of 165 g. of chloral hydrate and 202 g. of toluene. The stirring was continued for 3 hours, and the viscous mass poured onto crushed ice. The crude product was washed with water and triturated with 200 cc. of alcohol. From 1200 cc. of alcohol, white platelets of 1,1-di-(*p*-tolyl)-2,2,2-trichloroethane, m.p. 89°, yield, 53%.

1,1-Di-(p-carboxyphenyl)-2,2,2-trichloroethane (VI). To a mixture of 76.6 g. of potassium dichromate, 26.6 g. of the preceding substance, and 150 cc. of water, was added, with stirring, 170 g. of concentrated sulfuric acid. When half of this quantity was added, the mixture began to warm up; it was heated to the boiling point, and the addition was continued at the boiling temperature. A viscous product precipitated. The reaction mixture was diluted with 1 liter of water, and the solid material ground, washed with 300 cc. of 5% sulfuric acid and water, and extracted with 200 cc. of 5% aqueous sodium hydroxide solution. The desired dicarboxylic acid was precipitated by means of dilute sulfuric acid and recrystallized from 50% alcohol or nitrobenzene; needles of m.p. 271–272° (dec.), yield 20%.

Anal. Calc'd for $C_{16}H_{11}Cl_3O_4$: C, 51.5; H, 2.9; Neut. equiv., 373.
Found: C, 52.0; H, 3.1; Neut. equiv., 374.

1,1-Di-(p-carboxamidophenyl)-2,2,2-trichloroethane (V). A mixture of 4 g. of the dicarboxylic acid and 12 cc. of thionyl chloride was refluxed for 3 hours. The excess chloride was removed by distillation and the remaining viscous yellow oil taken up in ether and added slowly to a concentrated aqueous ammonia solution. The yellowish precipitate was washed with water and recrystallized from methanol or glacial acetic acid; transparent platelets of m.p. 227° (dec.), yield, quantitative.

Anal. Calc'd for $C_{16}H_{13}Cl_3N_2O_2$: C, 51.7; H, 3.5; N, 7.5.
Found: C, 52.0; H, 3.7; N, 7.4.

1,1-Di-(3'-nitrophenyl)-2,2,2-trichloroethane. From the glacial acetic acid mother

liquors of the di-*para*- nitro compound, colorless crystals separated upon standing. They were recrystallized several times from the same solvent and formed well-shaped prisms of m.p. 118°.

Anal. Calc'd for $C_{14}H_9Cl_3N_2O_4$: C, 44.9; H, 2.4.

Found: C, 44.3; H, 2.6.

1,1-Di-(3'-nitrophenyl)-2,2-dichloroethylene. A mixture of 1.8 g. of the preceding substance with a solution of 0.5 g. of potassium hydroxide in 25 cc. of methanol was boiled under reflux for 4 hours. The reaction product crystallized upon cooling, and was filtered, washed with water, dried, and recrystallized from butanol; m.p. 128–129°, yield 82.3%.

Anal. Calc'd for $C_{14}H_8Cl_2N_2O_4$: C, 49.2; H, 2.3.

Found: C, 49.8; H, 2.0.

Oxidation. To a boiling solution of 0.5 g. of the nitroethylene in 5 cc. of glacial acetic acid, 1 g. of chromic acid in 5 cc. of the same solvent was slowly added, and the boiling was continued for 4 hours. The reaction product was poured onto crushed ice; the oil which separated, solidified spontaneously; from glacial acetic acid, plates which showed the correct m.p. 160° of *3,3'-dinitrobenzophenone.*

1,1-Di-(3',5'-diiodo-4'-aminophenyl)-2,2,2-trichloroethane. To a solution of 1 g. of the diamino compound in 5 cc. of glacial acetic acid, was added gradually a solution of 2.5 g. of iodine monochloride in 5 cc. of the same solvent. The reaction was accompanied by a rise in temperature. After 12 hours, the mixture was diluted with water, filtered, and the solid material washed with sodium bisulfite solution; from methyl alcohol, m.p. 145° (dec.).

Anal. Calc'd for $C_{14}H_9Cl_3I_4N_2$: C, 20.5; H, 1.2; N, 3.4.

Found: C, 20.7; H, 1.4; N, 3.8.

1,1-Di-(4'-trichloroacetylaminophenyl)-2,2,2-trichloroethane. To an ice-cold solution of 3.2 g. of the diamino compound, 2 g. of pyridine, and 40 cc. of chloroform, was added, drop by drop, 3.6 g. of trichloroacetyl chloride. After 12 hours, the clear reaction mixture was treated with water, and the solvent evaporated to dryness. The residue was triturated with petroleum ether and recrystallized from a mixture of the same solvent with butyl alcohol; m.p. 198.5°, yield 58%.

Anal. Calc'd for $C_{18}H_{11}Cl_9N_2O_2$: C, 35.6; H, 1.8; N, 4.6.

Found: C, 36.2; H, 1.7, N. 4.5.

From *benzene*, the product crystallizes with 1 mole of the solvent. This solvate melts at 142° with gas evolution, solidifies again, and melts finally at 198°.

Anal. Calc'd for $C_{18}H_{11}Cl_9N_2O_2 \cdot C_6H_6$: C, 42.1; H, 2.4; N, 4.1.

Found: C, 42.4; H, 4.2; N, 4.6.

Dye-stuff from 1,1-di-(4'-aminophenyl)-2,2,2-trichloroethane and 2-hydroxy-3-naphthoic acid. A solution of 3.15 g. of the diamino compound in a mixture of 6 cc. of concentrated hydrochloric acid and 20 cc. of water was diazotized at 0° with a solution of 1.4 g. of sodium nitrite in 4 cc. of water. By addition of 0.5 g. of sodium carbonate, the solution was neutralized and it was dropped at ice temperature into a solution of 3.6 g. of 2-hydroxy-3-naphthoic acid and 2.12 g. of sodium carbonate in 40 cc. of water. By filtration and thorough washing with water, there was obtained 7.5 g. of the dye-stuff in the form of a red powder, which crystallized slowly from a mixture of xylene or isoamyl alcohol with nitrobenzene, and melted then at 207° (with decomposition).

Anal. Calc'd for $C_{36}H_{23}Cl_3N_4O_6$: C, 60.6; H, 3.2; N, 9.1.

Found: C, 60.7; H, 3.6; N, 9.1.

Dye-stuff from 1,1-di-(4'-aminophenyl)-2,2,2-trichloroethane and 2-hydroxy-3-naphthanilide. The diazonium salt, prepared and neutralized as in the previous example, was coupled at 0° with 50 cc. of an aqueous solution of 5.3 g. of 2-hydroxy-3- naphthanilide, containing 3 cc. of 30% sodium hydroxide solution. The reaction product was treated with dilute hydrochloric acid and the solid recrystalized from nitrobenzene diluted with some butanol; clusters of red crystals which melt at 235–240° (dec.).

Anal. Calc'd for $C_{48}H_{33}Cl_3N_6O_4$: C, 66.7; H, 3.8; N, 9.7.

Found: C, 67.4; H, 4.3; N, 10.0.

Dye-stuff from 1,1-di-(4'-aminophenyl)-2,2,2-trichloroethane and methyl 2-hydroxy-3-naphthoate. The diazonium solution, prepared as in the preceding examples, was added to a solution of 4.2 g. of methyl 2-hydroxy-3-naphthoate in 30 cc. of water containing 3 cc. of 30% sodium hydroxide solution. A red product precipitated. The reaction mixture was acidified and the product washed with water; recrystallized from nitrobenzene, m.p. 185–190° (dec.).

Anal. Calc'd for $C_{37}H_{27}Cl_3N_4O_6$: C, 64.3; H, 3.8.
Found: C, 63.9; H, 3.8.

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[Contribution from the Research Department, Phillips Petroleum Company]

PREPARATION OF 1-BUTENE LABELLED WITH C^{14} IN THE FOUR POSITION

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1-Butene labelled with C^{14} is a useful hydrocarbon for study of numerous hydrocarbon reactions. The molecule is large enough for its reactions to be typical of longer-chain olefins—for example it can undergo both double-bond and skeletal isomerization—and yet the products are in general readily analyzed by infrared absorption. Although for many purposes the position of the labelled carbon might be immaterial we elected to use a synthesis which places the C^{14} unambiguously in the 4-position.

Since the method is straightforward and simple and yields a product of high purity, the preparation is described in some detail along with data on yields and by-products.

The reactions employed are indicated in the following diagram:

$$\overset{*}{C}H_3OH \xrightarrow{HI} \overset{*}{C}H_3I \xrightarrow[\text{ether}]{Mg}$$

$$\overset{*}{C}H_3MgI \xrightarrow{CH_2{=}CH{-}CH_2Br} CH_2{=}CH{-}CH_2\overset{*}{C}H_3$$

Methyl iodide was prepared by the method of Norris (1) and the reaction yielding 1-butene was carried out following the method of Lucas (2). The over-all yield was 63%, 4 grams of material being obtained of activity such that a thick sample ($BaCO_3$) 7/8″ in diameter gave 4000 counts per minute when analyzed in the usual manner with an end-window G–M tube of window thickness 2 mg./cm^2. In a "cold-run" closely similar to the final preparation of labelled butene, the product was scanned with infrared and the absorption spectrum was found to be indistinguishable from that of 1-butene.[1] The impurities were, therefore, less than 1% *n*-butane, 1% isobutane, 0.5% 2-butenes, and 0.5% isobutene. Combined C_4 impurities were less than 1%. Starting material was one-quarter millicurie of labelled methyl alcohol obtained from Oak Ridge through the Atomic Energy Commission.[2]

EXPERIMENTAL

The *apparatus* is indicated diagrammatically in Fig. 1. The reaction vessel, A, was equipped with a cold finger, a modified dropping-funnel and a side-tube reaching to the bottom of the reaction flask. The latter tube could be used for introduction of inert gas or

[1] Research Grade 1-butene, 99.7% pure, Phillips Petroleum Co.

[2] A second run has been completed with three-quarters millicurie of starting material. The yield of 1-butene and the recovery of radioactivity were about the same as in the previous run; but the product was diluted with 1-butene after distillation to provide ten ampoules of labelled material, each containing one gram of 1-butene and 0.05 millicurie of C^{14}.

for siphoning off liquid contained in the flask. Stirring was accomplished magnetically by means of a small glass-enclosed iron bar placed inside the flask and a horse-shoe magnet outside.

Methyl iodide. One ml. (0.8 g.) of methyl alcohol containing one-quarter millicurie had been transferred to tube C in a dilution carried out previously. Then 3.13 g. of additional methyl alcohol (unlabelled) was weighed into flask A which was cooled in a Dry Ice cooling-mixture and evacuated. The active methyl alcohol was then distilled into A. Finally, 76.5 g. of 57% HI (sp. gr. 1.7) was added to A through the dropping-funnel and the line was

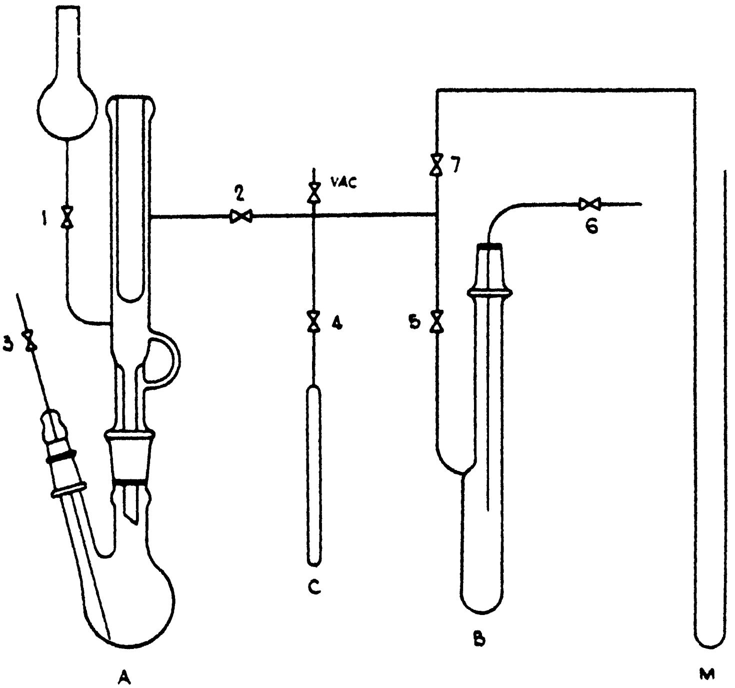

FIG. 1

filled with dry nitrogen. Flask A was heated in a water-bath following a definite schedule arrived at in cold runs:

0–45 minutes	50–55°	Cold finger filled with ice
45–80 minutes	55–65°	Cold finger not cooled
80–110 minutes	65–70°	Cold finger not cooled
110–140 minutes	70–100°	Cold finger not cooled

During the heating a slow stream of nitrogen was passed through the line *via* the side-tube of flask A and collected in a gas bottle attached to the outlet of B. Flask B was cooled in Dry Ice to condense methyl iodide and any unchanged methyl alcohol. On completion of the heating interval flask B was opened and 7 g. of anhydrous calcium chloride was added to absorb both water and unchanged methyl alcohol. After standing overnight the methyl iodide was distilled into tube C which was previously calibrated. The volume of CH_3I, 6.8 ml. at 20°C, indicated a yield of 88%. The residue in B was dissolved in water and siphoned into a bottle for subsequent examination.

Methyl magnesium iodide. Magnesium ribbon, free of oxide (2.8 g.) and 17.7 g. of anhydrous ether[3] were placed in flask A, which was cooled and evacuated. With Dry Ice and

[3] Analytical reagent, Mallinckrodt Chemical Works.

acetone in the cold finger and with ice-water on A the methyl iodide was distilled into A at the rate of 6.5 grams/hour. The ice-bath was frequently removed to permit stirring. Reaction started immediately and was smooth throughout. After standing overnight the methylmagnesium iodide was siphoned off and simultaneously filtered through glass wool using another flask similar to A. Flask A was washed with three 15-ml. portions of ether.

Flask A-2, containing filtered methylmagnesium iodide, was joined to the line while a slow stream of nitrogen was passed through and the flask heated to 130° using the following schedule for boiling off ether.

0–40 minutes	65–100°
40–60 minutes	100–120°
60–80 minutes	120–130°

TABLE I

DISTILLATION OF LABELLED 1-BUTENE

FRACTION	BOILING RANGE	WT., G	MEASURED ACTIVITY OF STANDARD THICK SAMPLE ($BaCO_3$), COUNTS/MIN.
I	C_3 and lower-boiling materials	0.1	15000
II	C_4	4.4	4000
III	C_5 and higher-boiling materials	1.8	230

TABLE II

RADIOACTIVITY BALANCE

FRACTION OR RESIDUE	ASSAY, *μcuries*	PER CENT OF ORIGINAL C^{14}
HI solution with undistilled CH_3OH or CH_3I	5	2.0
$CaCl_2$ solution with CH_3OH and CH_3I	6	2.4
CH_4 from CH_3MgI	7	2.8
Fraction I from distillation	12	4.8
Fraction II (1-butene)	163	65.3
Fraction III (C_{5+}; possibly also ether and allyl bromide)	3	1.2
Loss, including errors in assays		21.5
		100.0

1-Butene. When evolution of ether became slow the reaction flask was cooled to 70°, crushed ice was placed in the cold finger, and 12.7 g. of allyl bromide[4] was added through the dropping-funnel at the rate of a few drops every half minute. The butene was collected in flask B which was cooled with a Dry Ice cooling-mixture. Pressure was maintained at atmospheric by passing a very slow stream of nitrogen into the side tube of flask A and out through flask B into a gas bottle.

The 1-butene was distilled under vacuum into an ampoule with a break-seal leaving only a trace of residue in flask B. The ampoule was sealed off and stored in a Dry Ice box for subsequent fractionation. The residue in flask A was treated with water to convert unchanged Grignard reagent to methane and the gas evolved was collected over water in a gas bottle. One hundred cc. of gas, obtained in this way, was diluted to 3 l. with methane.[5]

The 1-butene was condensed in a small distilling-apparatus and divided into three frac-

[4] Halogen Chemicals, boiling range 69.0–70.5°.

[5] Research Grade methane, 99.6% pure, Phillips Petroleum Co.

tions using the customary procedures for light-hydrocarbon distillation. Amounts, boiling ranges and activities of the three fractions are given in Table I.

Radioactivity balance. Examination of residues and by-products yielded the information given in Table II. Calculations of absolute activity were made on the basis that a thick sample of $BaCO_3$ has measurable activity equivalent to that of 3.6 mg./cm.^{2} without self absorption. Corrections for window and air absorption and for geometry were made following Reid (3).

Acknowledgments. These procedures were suggested by Professor John Sowden of Washington University who also advised on techniques in handling the radioactive materials. Professor J. W. Kennedy advised on techniques and made available the facilities of the Radiochemical Laboratory, Washington University, for this work. Dr. W. H. Yanko also assisted with the Grignard synthesis.

SUMMARY

1-Butene of high purity has been prepared in 63% yield from methyl alcohol containing carbon-14. The method and apparatus are described in detail including examination of by-products.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF KANSAS]

STUDIES ON THE ACID HYDROLYSIS OF α-HALOGENATED PYRIDINE COMPOUNDS[1]

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During a recent investigation of the chemistry of Coenzyme I and II the methiodides of 2- and 6-fluoronicotinamides were required. Reaction of the corresponding fluoronicotinamides with excess methyl iodide under pressure, followed by recrystallization from water, was found to give only the hydroxynicotinamides. When ethyl iodide was substituted for methyl iodide no reaction whatever occurred. The corresponding bromonicotinamides were unreactive toward either halide.

It was further observed that the successful preparation of the fluoronicotinamides appeared to be dependent upon the presence of a small amount of thionyl chloride. Frequently, when all traces of thionyl chloride were removed from the acid chloride, hydrolysis occurred during the initial recrystallization from water. When this was not done, hydrolysis did not occur. Hydroxynicotinamides were also isolated as by-products of the successful preparation of the amides. No such difficulty was observed in the preparation of 2-bromo- or 6-chloro-nicotinamides.

Because of these observations, a study of the relative ease of acid hydrolysis of various halogens when substituted in the α-position in pyridine was undertaken. Although it has been known for some time that α- and γ-halogen on pyridine is more reactive than aromatic halogen, relatively little systematic work has been done on the subject. Skraup (1) found that α-chloroquinoline was hydrolyzed to carbostyril by dilute acid at 120°. Later Decker (2) found that ten minutes at the boiling point sufficed for the acid hydrolysis of 8-nitro-2-chloroquinoline. He suggested that the formation of the strongly positive quaternary nitrogen was in part responsible for the ease of hydrolysis. The results of Wibaut (3), who found that N-4-pyridyl-4-chloropyridinium chloride and its bromine analog are hydrolyzed to the corresponding pyridones by dilute acid at room temperature, support this hypothesis. Räth (4) has reported that 2-chloropyridine, 5-nitro-, 5-chloro-, and 3-chloro-5-nitro- 2-chloropyridine are all hydrolyzed to the corresponding pyridones by hydrochloric acid at 150°. Bobranski (5) found that 4-chloroquinoline was converted to 4(1)-quinolone on acid treatment at 150°, and Wibaut (3) reported that 2,6-dibromopyridine could be cleaved by acid at 150° but not at 100°.

These facts suggest that while α- and γ-halogen on the pyridine nucleus is somewhat activated, the activation is not so great as some authors have supposed in the past. The electronic similarity of pyridine and nitrobenzene proposed by

[1] We are indebted to the United States Public Health Service for a fellowship granted to one of us (H. L. B.).

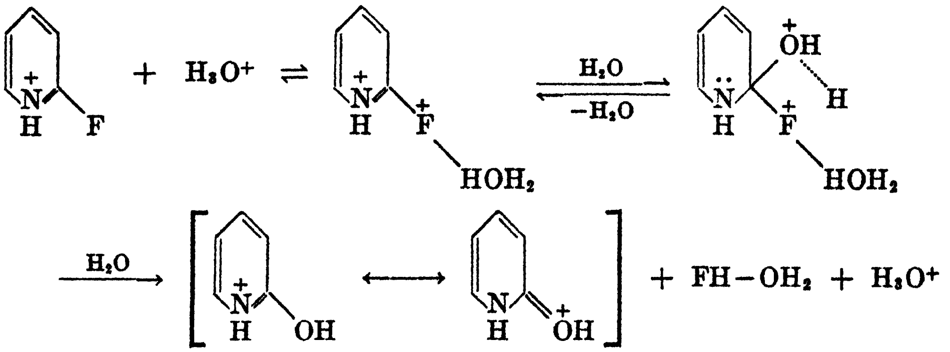
Erlenmeyer[2] (6) on biochemical grounds provides a frame of reference from which to interpret the reactivity of α- and γ-halogen. On this basis the variation in lability becomes more intelligible. Just as the chlorine of *o*- or *p*-nitrochlorobenzene is more reactive than that of chlorobenzene, so is that of α- or γ-chloropyridine. Just as the halogen of 2,4-dinitrochlorobenzene is more reactive than that of nitrochlorobenzene, so is the halogen of 8-nitro-2-chloroquinoline more reactive than that of 2-chloroquinoline.

Although Wibaut (3) has reported the hydrolysis of 2,6-dibromopyridine to 2-bromo-6-hydroxypyridine by means of alcoholic sodium hydroxide, on the whole alkaline hydrolysis is much less readily effected, as the experimental results reported below will show. None of the fluoro- or bromo-nicotinic acids or picolines showed appreciable alkaline hydrolysis. This is to be expected since the activating quaternary nitrogen is present in acid but not in basic solution. In confirmation it was found that 2-iodo-3-methyl- and 2-iodo-5-

TABLE I

RESULTS OF HYDROLYTIC EXPERIMENTS

HYDROLYSIS	NO HYDROLYSIS
2-Fluoropyridine	2-Chloropyridine
2-Fluoro-3-methylpyridine	2-Bromopyridine
2-Fluoro-5-methylpyridine	2-Bromo-3-methylpyridine
2-Fluoronicotinic acid	2-Bromo-5-methylpyridine
6-Fluoronicotinic acid	
2-Bromonicotinic acid	
6-Bromonicotinic acid	
2-Chloroquinoline	



methyl-pyridine ethiodides were readily hydrolyzed to the corresponding N-ethylpicolones in good yield by means of warm sodium hydroxide solution[3].

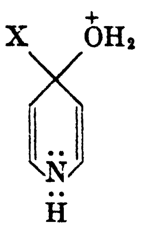
Hydrolysis with 6 *N* hydrochloric acid for twenty-four hours was selected as the standard treatment. Increasing the time to forty-eight or seventy-two hours

[2] N-diethyl *m*-nitrobenzamide was found to possess the same analeptic action as the corresponding pyridine derivative. Also *o*-sulfanilamidonitrobenzene was found to possess antibacterial activity comparable to that of sulfapyridine.

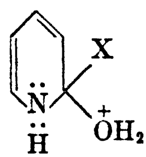
[3] The experimental details will be found in a paper now in press.

did not change the results summarized in Table I. In all cases the corresponding hydroxy compounds were isolated. While all of the fluoro derivatives were hydrolyzed, the only bromo compounds which were hydrolyzed were those which contained an additional activating group. The results are consistent with the following electronic mechanism:
The lesser tendency of chlorine and bromine to form hydrogen bonds as well as their lower electronegativity both operate to decrease the lability of these halogens as compared with fluorine[4]. When, however, another labilizing group is present, as in the bromonicotinic acids or in 2-chloroquinoline, hydrolysis does occur.

The same considerations do not seem to apply to γ-halogen, which is in general much more reactive. Thus moist γ-chloropyridine (7) is converted on distillation to γ-pyridone hydrochloride. Also γ-fluoropyridine (8) cannot be isolated because of its rapid conversion to N-γ-pyridyl-γ-pyridone. Presumably this is due to the greater resonance stabilization of the *p*-quinoidal type intermediate structure (I) as compared with the *o*-quinoidal type structure (II).[5]



(I)



(II)

The formation of the hydroxynicotinamides in the reaction of the fluoronicotinamides with methyl iodide can easily be correlated with the above results. A considerable decomposition of methyl iodide occurs at 80° and the initial aqueous solutions are sufficiently acidic (pH < 1) to effect the observed hydrolysis.

As indicated in the experimental results, an acidic by-product was present during the first recrystallization from water. Unless precautions were taken to limit the period of heating and the amount of water to a minimum the fluoroamides would not precipitate from the acidic solution. Concentration of the solution did not give the original fluoroamides but the hydroxyamides. The acidity increases on concentration, suggesting an autocatalytic hydrolysis which proceeds readily once the solution is even mildly acidic. Once freed of this acidic by-product the fluoroamides are stable toward water. The hydroxyamides must be considered to be artifacts.

Surprisingly, attempts to convert 6-bromonicotinic acid to the acid chloride

[4] Added in press. Such an acid catalysis has recently been reported for the benzyl fluorides by Miller and Bernstein, *J. Am. Chem. Soc.*, **70**, 3600 (1948).

[5] See Waters (9) for a discussion of the significance of the transition state in substitution reactions.

with either thionyl chloride or oxalyl chloride under a variety of conditions resulted in halogen exchange. Ammonolysis of the crude acid chloride so formed gave only 6-chloronicotinamide. Attempted ammonolysis of methyl 6-bromonicotinate with alcoholic ammonia led to recovery of the original ester.

EXPERIMENTAL[6, 7]

Preparation of intermediates. The 2- and 6-fluoro-3-methylpyridines, nicotinic acids, and nicotinamides were prepared by the method of Minor, Hawkins, *et al.* (10). 2-Bromo-3-methylpyridine and 2-bromo-5-methylpyridine were prepared in 87% and 80% yields, respectively, by the methods of Allen (11) for the preparation of 2-bromopyridine.

Best results were obtained when a stiff, tantalum Hershberg stirrer was used, as the mixtures become quite thick during the course of the reaction. Less concentrated hydrobromic acid (40%) may be used in place of the 48% acid, but the results are not so satisfactory (*ca.* 75–80% yields). The *2-bromo-3-methylpyridine* boiled at 82–86° at 9 mm. Mariella (12) has reported the boiling point as 76–77° at 7 mm.

* *Anal.* Calc'd for C_6H_6BrN: N, 8.2. Found: N, 8.3, 8.5.

The *2-bromo-5-methylpyridine* boiled at 73–77° at 8 mm.

* *Anal.* Calc'd for C_6H_6BrN: N, 8.2. Found: N, 8.3, 8.5.

Preparation of 6-bromonicotinic acid. Exactly 122.3 g. of 2-bromo-5-methylpyridine was added to a solution of 278 g. of potassium permanganate in 3 l. of water. The mixture was stirred under reflux for five hours. Then 15 g. of potassium permanganate was added and refluxing was continued for an additional hour. The mixture was distilled until all of the unreacted 2-bromo-5-methylpyridine (about 45 g.) was recovered. The hot solution was then filtered and the precipitated manganese dioxide was twice stirred with boiling water and re-filtered. The combined filtrate and washings were concentrated to 600 ml.,[8] filtered, and acidified with concentrated hydrochloric acid. About 90–100 g. of crude acid was obtained. After recrystallization from water it melted at 193.0–193.9°.

* *Anal.* Calc'd for $C_6H_4BrNO_2$: N, 6.9. Found: N, 7.0, 7.1.

The crude acid may be directly converted to the amide. The acid was characterized as the methyl ester. Esterification by means of diazomethane gave much better results than the use of methanol with either dry hydrogen chloride or sulfuric acid as catalyst. To an ether solution of 0.1 mole of diazomethane a slight excess of the acid as a slurry in ether was added gradually with shaking until the yellow color vanished. The ether solution was washed with 10% sodium carbonate solution, then with saturated brine, and distilled to give 18.1 g. (84%) of the *methyl ester* boiling at 107–110° at 4 mm. An analytical sample, m.p. 108.5–110.0°, was obtained by vacuum sublimation.

Anal. Calc'd for $C_7H_6BrNO_2$: N, 6.5. Found: N, 6.4, 6.3.

The *2-bromonicotinic acid* was prepared in exactly the same way in the same yield. After recrystallization from water it melted at 249.1–250.4°.

* *Anal.* Calc'd for $C_6H_4BrNO_2$: N, 6.9. Found: N, 7.0, 7.1.

The acid was characterized as the *methyl ester* prepared in the same way as its isomer. A 92% yield of ester boiling at 95–97° at 1.4 mm. was obtained. After recrystallization from dilute alcohol it melted at 107.2–108.3°.

Anal. Calc'd for $C_7H_6BrNO_2$: N, 6.5. Found: N, 6.3

Attempted preparation of 6-bromonicotinamide. A mixture of 30 g. of 6-bromonicotinic acid and 300 ml. of thionyl chloride was refluxed for twenty hours. Excess thionyl chloride

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[6] All melting points corrected, all boiling points uncorrected.

[7] All analyses by Clark Microanalytical Laboratories, Urbana, Illinois, unless starred. Starred analyses are by Arlington Laboratories, Fairfax, Virginia.

[8] The fact that neither the fluoro- nor the bromo-nicotinic acids hydrolyzed during the concentration of these alkaline solutions is evidence for the absence of any rapid alkaline hydrolysis reaction.

was removed *in vacuo*. The residue was added as a slurry in dioxane or benzene to 75 ml. of cold, stirred concentrated ammonium hydroxide. The mixture was stored overnight and then filtered to give 26.2 g. of crude *6-chloronicotinamide*. After recrystallization from water it melted at 213.5–214.2°. Kushner (13) reported the m.p. as 212–213°.

Anal. Calc'd for $C_6H_5ClN_2O$: C, 45.9; H, 3.2; Cl, 22.6; N, 17.9.
Found: C, 45.7; H, 3.4; Cl, 22.7; N, 17.7.

The use of smaller amounts of thionyl chloride and shorter reflux periods, as well as dilution with benzene, served only to decrease the yield of 6-chloronicotinamide. Treatment of the acid with oxalyl chloride in benzene gave a quantitative yield of the chloroamide, even when the reflux period was shortened to four hours.

In an attempted ammonolysis of methyl 6-bromonicotinate, a mixture of 1 g. of the ester, 10 ml. of concentrated ammonium hydroxide, and 10 ml. of methanol was refluxed for eighteen hours. The solution was concentrated and cooled. The starting ester, m.p. 108.3–110.2°, crystallized from the solution. Extension of the reflux period had no appreciable effect on the results. In view of the results of Kushner (13) with the corresponding methyl 6-chloronicotinate, use of more drastic conditions is precluded.

2-Bromonicotinamide. This product was prepared in 80% yield by treatment of 2-bromonicotinic acid with thionyl chloride according to the procedure described for the attempted preparation of 6-bromonicotinamide. It exhibited an unusual melting point behavior. It softened appreciably at 140°, resolidified at 147°, melted at 171–172°, resolidified at 175–176° and finally decomposed at about 260°.

Anal. Calc'd for $C_6H_5BrN_2O$: C, 35.8; H, 2.5.
Found: C, 35.5; H, 2.6.

2-Fluoropyridine. This product was prepared in good yield according to the method of Roe and Hawkins (8). 2-Fluoropyrimidine could not be successfully prepared in this manner. 2-Chloropyridine, 2-bromopyridine, and 2-chloroquinoline were Eastman products.

Reaction of substituted amides with ethyl iodide. In each case a 2-g. sample of amide was heated with 25 ml. of ethyl iodide for twelve hours at 110° in a sealed tube. The ethyl iodide was then removed by evaporation and the residue recrystallized from water. In all cases the original amide was recovered in good yield.

Reaction of the amides with methyl iodide. These reactions were carried out in a sealed tube at 80°. The chloro- and bromonicotinamides were recovered unchanged. The behavior of the fluoroamides was quite different. The 2-fluoroamide dissolved in the methyl iodide on heating but later separated out again as a red oil. Immediate evaporation after solution had occurred gave only the original amide. After twelve hours of heating the methyl iodide was removed by distillation, the residue was taken up in water (very soluble) and extracted with ether to remove free iodine. The solution was concentrated somewhat, cooled and the crystalline product filtered off. The compound was recrystallized from water. The solubility was much lower at this stage. The behavior of 6-fluoronicotinamide was similar except that it did not dissolve in the methyl iodide. The *2-hydroxyamide* sintered at 265° and melted at 270.1–272.0°.

Anal. Calc'd for $C_6H_6N_2O_2$: C, 52.1; H, 4.3; N, 20.3.
Found: C, 51.9; H, 4.1; N, 20.9.

Acid hydrolysis gave the known *2-hydroxynicotinic acid* melting at 260.0–261.2°, with gas evolution, after recrystallization from water. Philips (14) reported 256°.

Anal. Calc'd for $C_6H_5NO_3$: C, 51.7; H, 3.6; N, 10.1.
Found: C, 51.4; H, 3.3; N, 10.1.

It was further identified as the *methyl ester*, m.p. 152.1–153.3°, prepared by the method of Kirpal (15) who reported m.p. 153°. The *6-hydroxyamide* melted at 313.0–314.4°.

Anal. Calc'd for $C_6H_6N_2O_2$: C, 51.9; H, 4.3.
Found: C, 52.0; H, 4.5.

Acid hydrolysis gave the known *6-hydroxynicotinic acid*, which sintered at 305–308° and melted at 309°. Von Pechmann (16) reported the m.p. 303°.

Anal. Calc'd for $C_6H_6N_2O_3$: C, 51.7; H, 3.6; N, 10.1.
Found: C, 51.7; H, 3.1; N, 10.0.

The acid was further identified as the *methyl ester*, m.p. 166.1–167.5°, prepared by the method described by Meyer (17), who reported the m.p. 164°.

Preparation of 2- and 6-fluoronicotinamides. When the preparation was carried out exactly as described by Minor, Hawkins, *et al.* (10) the fluoroamides were easily obtained. Working up the mother liquors gave a small amount of the corresponding hydroxyamides. Frequently, however, when the last traces of thionyl chloride were removed by the repeated addition and vacuum distillation of dry benzene the hydroxyamides were the sole products. Judging from the solubility behavior, the actual hydrolysis seemed to occur during the first recrystallization from water. The *p*H of the freshly prepared solution was 6.4. If the solution was concentrated, the *p*H dropped to 3.9 within a short time. Although on smaller scale runs (*ca.* 2 g.) the fluoroamides did not hydrolyze during the brief period required to concentrate the solution, nevertheless hydrolysis did occur during the much longer period required for large runs (*ca.* 70 g.) when carried out on the steam-bath. If solution was effected with a minimum of water and prompt cooling employed, pure fluoroamides were obtained in good yield.

Acid hydrolysis of the compounds in Table I. One-gram samples of each compound were refluxed for twenty-four hours with 10 ml. of 6 *N* hydrochloric acid. Results were as follows:

Bromo- and fluoro-nicotinic acids. On cooling, the hydroxynicotinic acids crystallized. The acids, after recrystallization from water, were identified by melting point and mixed melting point.

2-Chloroquinoline. The product was *2-hydroxyquinoline*, m.p. after recrystallization from alcohol 199.0–200.1°, which separated in quantitative yield from the acid solution. Morgan (18) reported the m.p. as 199–200°.

2-Fluoro-, 2-chloro-, 2-bromo-, 2-fluoro-3-methyl-, 2-fluoro-5-methyl-, 2-bromo-3-methyl-, and 2-bromo-5-methyl-pyridines. The acid solutions were made alkaline with sodium carbonate. In all cases except that of the fluoro derivatives the solutions were repeatedly extracted with ether. Chloroform was used for the fluoro derivatives. The extracts were washed, dried over sodium sulfate, and concentrated. The chloro and bromo derivatives were recovered unchanged in almost quantitative yield. From 2-fluoropyridine, *2(1)-pyridone*, b.p. 290–295° (730 mm.), m.p. 106–107°, was obtained in 60% yield. From the fluoropicolines, the corresponding picolones were obtained in 66% yield. 3-Methyl-2-(1)-pyridone,[9] after sublimation *in vacuo*, melted at 138.0–139.5°. Seide (19) reported the m.p. 140°.

Anal. Calc'd for C_6H_7NO: N, 12.8. Found: N, 12.7, 12.8.

5-Methyl-2(1)-pyridone, after recrystallization from benzene, melted at 183.0–184.1°.

Anal. Calc'd for C_6H_7NO: N, 12.8. Found: N, 12.8.

Alkaline hydrolysis studies. Two gram samples of 2-fluoro-3-methylpyridine and 2-bromo-3-methylpyridine were refluxed with 10 ml. of 25% sodium hydroxide solution in water or 50% alcohol for four days. No appreciable reaction occurred in any case, the starting material being recovered in each instance.

SUMMARY

1. A study has been made of the reactions of methyl and ethyl iodides with 2-bromo, 6-chloro- and 2- and 6-fluoro-nicotinamides. N-alkylation could not be effected in any instance; however, after treatment with methyl iodide, the fluoronicotinamides underwent hydrolysis to the corresponding hydroxynicotinamides during the course of the subsequent isolation procedure. This hydrolysis

[9] This compound has also been isolated as a by-product of the preparation of 2-fluoro-3-methylpyridine by the procedure of ref. 10.

was catalysed by acidic products formed during the attempted methylation reaction.

2. Comparative studies have shown that fluorine substituted in the α-position on the pyridine nucleus is more labile toward acid-catalysed hydrolysis than either chlorine or bromine.

3. A mechanism which accounts for the comparative ease of acid-catalysed hydrolysis of α-fluoropyridines is proposed.

LAWRENCE, KANSAS.

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[CONTRIBUTION FROM THE RADIATION LABORATORY AND DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA]

THE SYNTHESIS OF TOLUENE-1,3,5-C^{14} AND OXALIC ACID-C^{14}; THE MECHANISMS OF THE REACTIONS[1]

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For the purpose of carrying out many types of tracer studies, it is necessary to have aromatic compounds labeled in the ring with isotopic carbon. A useful intermediate for the synthesis of such compounds would be toluene[3]. At the suggestion of Professor Melvin Calvin, the authors have investigated the feasibility of synthesizing toluene-C^{14} by decarboxylating uvitic acid (II), prepared from pyruvic acid-α-C^{14} *via* methyldihydrotrimesic acid (I). A valuable feature of this scheme is the formation of oxalic acid, a useful compound, which should be labeled if the scheme which has been postulated (1) for the condensation of pyruvic acid to methyldihydrotrimesic acid is correct. Although there is no reason to doubt the correctness of the essential features of this postulate, it was thought to be of interest to apply those checks which tracer technique affords, since there are still comparatively few instances in which mechanisms formulated from considerations of the classical types have been directly checked with isotopic carbon. Accordingly, the specific activities of the intermediate compounds have been determined, and the mechanisms of all the reactions involved in the synthesis checked with respect to the fate of the tracer carbon atom.

The reaction sequence is described in Fig. 1, which includes the previously postulated (1) course of the reactions leading to the formation of uvitic acid (equations A and B). It will be shown that equation B is in error with respect to the minor products. Positions expected to be labeled are marked with an asterisk.

The radioactivity measurements are recorded in Table I. The molar specific activity to which reference is made in the heading of the third column is the specific activity of the compound multiplied by its molecular weight. The ratios are calculated with the molar specific activity of the methyldihydrotrimesic acid as the denominator; each ratio has been multiplied by three to obtain integral values. Each value so calculated expresses, for the compound to which it refers, the number of carbon atoms in the molecule which were ketonic carbon atoms in pyruvic acid, assuming that three of the ketonic atoms have been incorporated into methyldihydrotrimesic acid. Why the specific activity of pyruvic acid is not made the denominator of the ratio will be made clear below. The

[1] This paper is based on work performed under Contract No. W-7405-Eng-48 with the Atomic Energy Commission in connection with the Radiation Laboratory, University of California, Berkeley.

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[3] *Note added in proof.* Subsequent to the submission of this paper for publication, a synthesis of toluene labeled with carbon 14 in position 1 has been reported by Fields, Leaffer, and Rohan [*Science*, **109**, 35 (1949)].

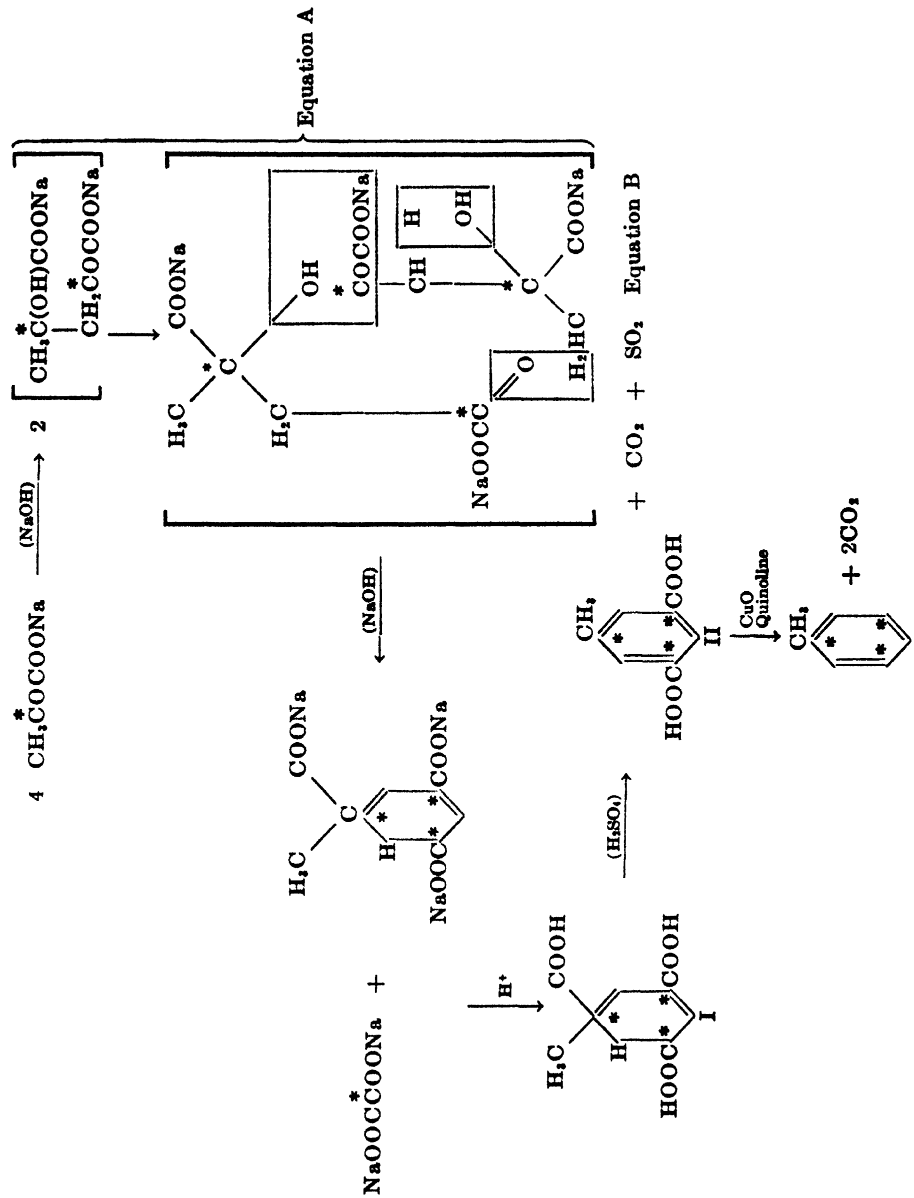

FIGURE 1

ratios show that for each ketonic carbon atom which appears in oxalic acid, three appear in methyldihydrotrimesic acid, and that these three are not lost in the succeeding reactions which lead to toluene. These facts are in accord with the mechanisms implied by the equations in Fig. 1. It is on the strength of this that the assignment of the positions of the tracer atoms has been made.

The molar specific activity ratio for pyruvic acid should be unity; actually, it is 2.08. The explanation of this discrepancy is contained in the activity totals tabulated in the fourth column of Table I. These numbers show that the sum of the total activities of the methyldihydrotrimesic acid, oxalic acid and residual

TABLE I

RADIOACTIVITY MEASUREMENTS ON THE REACTION PRODUCTS

COMPOUND	SP. ACT. CTS./MIN./MG.	MOLAR SP. ACT. / MOLAR SP. ACT. MDTA	TOTAL ACT. AS % OF INITIAL
Undiluted active pyruvic acid	9420	—	100
Diluted pyruvic acid	427	2.08	100
Methyldihydrotrimesic acid monohydrate	223	3.00	24.5
Oxalic acid dihydrate	150	1.04	11.3
Syrup	464	—	16.5
Barium Carbonate I[a]	66.3	—	8.82
Uvitic acid	302	2.98	23.7
Barium Carbonate II	0.68	∼0	0.0022
Barium Carbonate III	0.049	∼0	0.0029
Toluene	589	2.98	21.0
Barium Carbonate IV	0.07	∼0	0.010

[a] For identification of the source of the barium carbonate specimens, see Experimental section.

syrup is only 52% of the total activity of the pyruvic acid. Since the total weight of these three substances accounts for substantially all of the pyruvic acid, the radioactive (undiluted) preparation must have contained radioactive impurity, which amounted to about 50% by weight.

Although it is clear from the total activity values in Table I that the impurity did not participate in the reactions under study, it was identified as a matter of interest. A potentiometric titration of the pyruvic acid gave an equivalent weight corresponding to 90% pyruvic acid; the impurity is, therefore, acidic, although only one break was detectable in the titration curve. The fact that the final residue of salts contained a small part (18%) of the missing activity means that the impurity is extracted from acid solution by ether, but only slowly. Since the syrup did not contain an appreciable amount of the activity extracted,

the impurity is a volatile substance, which was lost wher the syrup was dried in vacuum. That the activity unaccounted for actually was lost from the syrup during its drying was verified by a confirmatory experiment, in which an aliquot of the syrup was assayed without being dried. In this repeat run, substantially all of the initial activity was accounted for; the amount in the methyldihydrotrimesic and oxalic acids was about the same as before, but that in the syrup was much higher.

The method used to synthesize the pyruvic acid[4] suggested that the impurity was acetic acid, as did the observations just recorded concerning its behavior. The identification was made by determining the Duclaux numbers of the acid distillable from the liquor obtained in the confirmatory experiment after removal of methyldihydrotrimesic and oxalic acids. The liquor was freed of chloride by treatment with silver oxide, then was filtered and adjusted to *p*H 3 with sulfuric acid. The Duclaux numbers are given in Table II. The specific activities of

TABLE II

DUCLAUX NUMBERS FOR THE CONTAMINANT

TOTAL VOLUME OF DISTILLATE, ML.	ACID CONTENT AS % OF TOTAL DISTILLED	% EXPECTED FOR ACETIC ACID
10	20.7	18.7
20	39.9	38.2
30	59.4	57.4
40	79.6	78.6
50[a]	100.0	100.0

[a] The distillation was interrupted when 50 ml. of distillate had been collected because the large amount of sodium sulfate present caused unmanageable bumping.

the first and last fractions of the distillate were found[5] to be 8.8×10^5 and 9.0×10^5 cts./min./meq. respectively; in contrast to these values the specific activity of the diluted pyruvic acid was 3.26×10^4 cts./min./meq. There was 0.799 meq. of acetic acid in the 50 ml. of distillate collected. This should be about 34% (2) of the acetic acid originally present in the liquor; from this it can be calculated that the liquor contained 7.2×10^5 cts./min. of acetic acid, and the undiluted pyruvic acid contained about 47% acetic acid by weight, a value in satisfactory agreement with the estimate of 50% mentioned earlier.

The Duclaux identification was confirmed by converting the acetic acid to its anilide. To a portion of the Duclaux distillate containing 11.1 mg. of active sodium acetate was added inactive acetic acid equivalent to 334 mg. of sodium

[4] We are indebted to Mr. R. M. Lemmon for the radioactive pyruvic acid. The method of synthesis, described in outline in another place [Calvin and Lemmon, *J. Am. Chem. Soc.*, **69**, 1232 (1947)] utilizes the following sequence of reactions:

$$CH_3\overset{*}{C}O_2H \rightarrow CH_3\overset{*}{C}OBr \rightarrow CH_3\overset{*}{C}OCN \rightarrow CH_3\overset{*}{C}OCO_2H$$

[5] By evaporating an aliquot of the solution on a glass disc and counting the sodium acetate directly. The amount of sodium acetate was small enough to reduce the self-absorption error to minor proportions.

acetate (both values were determined by titration). Sodium acetate was obtained by evaporating the solution and was converted to acetanilide; the purified derivative had a specific activity of 264 cts./min./mg.; calculated, 212. The discrepancy can reasonably be attributed to a slightly low value in the direct count of sodium acetate.

It was found that in the formation of uvitic acid (equation B) methyldihydrotrimesic acid loses its carboxyl carbon atom as carbon monoxide, not carbon dioxide as reported in the earlier work of Wolff. That the gas evolved is carbon monoxide is shown by the fact that very little barium carbonate, and still less sulfite, was recovered from alkali through which the gas had passed; by passage over hot copper oxide, however, carbon dioxide was formed in essentially quantitative yield.

In order for methyldihydrotrimesic acid to form uvitic acid by loss of carbon dioxide, the extra hydrogen atom attached to the number two position of the ring must be disposed of in some way; the opinion expressed in the earlier work is that a certain amount of di- and tetra-hydrouvitic acid, and perhaps analogous methyltrimesic acids are formed. Such materials were thought to compose the bulk of certain syrups obtained under various decarboxylation conditions, although in general the syrups were difficult to work with and this fact precluded the isolation of pure compounds from them. The high yield of uvitic acid obtained when concentrated sulfuric acid is used as the decarboxylation catalyst is stated (3) to be due to its ability to oxidize the extra hydrogen and thereby prevent the formation of the hydrogenated acids. We have shown, however, that the sulfuric acid does not function in the decarboxylation as an oxidizing agent, yet the yield is quantitative. The analytical method used in the earlier work to identify the evolved gas must have been faulty, and the formation of di- and tetra-hydro acids in the reaction is therefore questioned.

EXPERIMENTAL

The radioactivity measurements were made by converting each organic sample to barium carbonate, which was mounted on a thin aluminum disc and counted with a G–M counter of the end-window type. The techniques employed are described elsewhere (4). All samples were counted long enough to reduce the statistical error to 1% or less.

Methyldihydrotrimesic acid and sodium oxalate from pyruvic acid. A 0.4802 g. portion of pyruvic acid-α-C^{14} which had been prepared[4] three weeks previously and stored in a refrigerator, was diluted with 10.124 g. of freshly distilled inactive pyruvic acid. The mixed acid (0.121 mole) was added dropwise to a solution of 22 g. (0.55 mole) of sodium hydroxide in 39 ml. of water, which was contained in an Erlenmeyer flask cooled in ice. The acid was added slowly to the solution, which was swirled to minimize local heating; the time required was about one-half hour. If local heating was excessive, or if the order of mixing was reversed, the yield was lowered. After the acid had been added, the pale yellow solution was heated 3.5 hours on a steam-bath. During this time, the color became deep orange and a precipitate of sodium oxalate appeared. The mixture was chilled and the sodium oxalate was collected on a sintered glass filter, where it was washed with three 5-ml. portions of 12 *M* sodium hydroxide. The bulk of the product was left in crude form for future use; the total amount of *oxalic acid* present was determined by permanganate titration of an aliquot to be 84% based on pyruvic acid.

To obtain a pure specimen for radioactivity assay, a portion of the crude dium oxalate

was converted to barium oxalate. The barium oxalate was dissolved in 3 *M* hydrochloric acid and the solution was evaporated to dryness on a steam-bath; then the residue was transferred to a small sublimation apparatus, and the oxalic acid was recovered by vacuum sublimation. The sublimed acid was crystallized twice from water and dried in air.

Methyldihydrotrimesic acid was precipitated from the filtrate left after removal of sodium oxalate by acidification with concentrated hydrochloric acid. The solution was cooled in ice during the acidification, and the acid was added slowly enough to prevent the temperature from rising above 60° as a precaution against decomposition of the methyldihydrotrimesic acid. A total of 50 ml. of hydrochloric acid was added, and the mixture was filtered. Sodium chloride was washed out of the white solid on the filter with 25 ml. of water in 3-4 ml. portions. The yield of acid, dried in high vacuum at room temperature, was 4.97 g. (67.5%). The principal impurity in the crude product was sodium chloride; purification of a sample for radioactivity assay was accomplished by crystallization from dilute ethanol at a temperature below 60°. The purified acid absorbs atmospheric moisture to form a monohydrate; drying in high vacuum gives the anhydrous compound. The radioactivity measurement was performed on the hydrate.

The filtrate left after removal of the methyldihydrotrimesic acid was subjected to continuous ether extraction for 8 hours. Evaporation of the ether left a syrup. When this was dried in vacuum a brittle brown material was obtained, which weighed 1.60 g.; it readily absorbed moisture from the atmosphere and again became syrupy. The material was burned *in toto* to determine its activity.[6]

The water solution from the ether extraction operation was neutralized with sodium hydroxide and evaporated. The activity of the residue was determined by heating an aliquot in a combustion train until all the carbonaceous materials were burned out of the rather large amount of salt present. The carbon dioxide was recovered as barium carbonate; this is referred to in Table I as Barium Carbonate I.

Uvitic acid from methyldihydrotrimesic acid. The decarboxylation apparatus consisted of a 125-ml. conical flask bearing two ground necks. The center neck was fitted with a compensated dropping-funnel, and the side neck carried a tube to conduct gas out of the flask. The tube extended a short distance into the flask and its end, which was drawn to small diameter, was bent up to serve as a spray trap. Provision was made for introducing a current of nitrogen, purified by passage through a preburner and a carbon dioxide absorber, into the system through the mouth of the dropping-funnel. A stopcock was situated in the line just ahead of the dropping-funnel. After leaving the flask, the gas passed through an absorber containing 1 *M* sodium hydroxide, then over copper oxide heated to 550°, and finally through a second absorber containing alkali. Atmospheric carbon dioxide was excluded from the system by a guard tube attached at the outlet.

Into the flask was placed 4.74 g. of dry crude methyldihydrotrimesic acid, and 20 ml. of concentrated sulfuric acid was placed in the funnel. The apparatus was assembled and the air was swept out with nitrogen. The stopcock was closed and the acid was run into the flask from the dropping-funnel. The mixture was heated in an oil-bath to 120° and decarboxylation commenced. When the initial evolution of carbon monoxide had subsided, the stopcock was opened to admit a current (25 cc./min.) of nitrogen, and the temperature of the bath was raised to 150° where it was held for 2 hours At the end of this time, the reaction mixture was cooled somewhat and poured into 100 ml. of water; this caused the uvitic acid to separate. The mixture was allowed to become hot, for by this procedure a product was obtained which was less difficult to filter than one prepared in the cold. The

[6] Several experiments were performed to investigate the behavior of this substance on decarboxylation. Subjection of the material to decarboxylating conditions gave, in the most favorable cases, mixtures of volatile liquid products which were largely olefinic in nature. The amounts formed were small and the mixtures were complex; consequently, no use except isotope recovery was made of the syrup.

crude, gray uvitic acid was collected on a sintered glass filter and carefully washed free of sulfate.[7] The yield of crude vacuum dried acid was 3.53 g. (100%).

To obtain a pure specimen for radioactivity assay, an aliquot was crystallized from dilute ethanol, with the use of charcoal, then crystallized again from dilute ethanol and dried under high vacuum. The *neutralization equivalent* of a specimen so purified was 90.5; calculated for anhydrous uvitic acid, 90.1.

To the alkali in each of the absorbers was added excess barium chloride solution and the precipitates were collected. The material from the first absorber weighed 0.149 g. after subtraction of the blank (3.9%). It was shown by permanganate titration to contain 6% barium sulfite; the rest was carbonate. This specimen is referred to in Table I as Barium Carbonate II.

After correction for blank, the barium carbonate obtained from the second absorber weighed 3.689 g. (96.8%). This specimen is referred to in Table I as Barium Carbonate III.

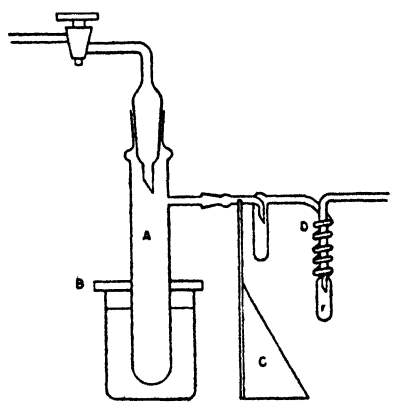

FIGURE 2. DECARBOXYLATION APPARATUS

Toluene from uvitic acid. The apparatus used for the decarboxylation of uvitic acid is shown in Fig. 2. The reaction vessel A is a 2 x 23-cm. Pyrex tube with a side arm, which terminates in a 10/30 ground joint, attached a short distance below the mouth. Provision is made for admitting purified nitrogen through a 24/40 ground joint, whose inner member has an extension which protrudes into the vessel to a point a few millimeters above the side arm. The tube is heated by a salt-bath; a Transite disc B prevents the silicone lubricant in the ground joints from becoming excessively hot. The vessel is connected to the unit D which consists of a fore-trap, whose capacity is about 5 ml., sealed to a second trap consisting of six turns of 7-mm. Pyrex tubing terminating in a 5 ml. receptacle *r*. The outlet of D is connected to a carbon dioxide absorber (not shown) containing 1 *M* sodium hydroxide. A guard tube to exclude atmospheric carbon dioxide completes the train. A Transite shield C protects D from the heat of a thermostatically controlled electric heater used to heat the salt-bath.

Vessel A was charged with 3.44 g. of dry crude uvitic acid, 0.50 g. of powdered cupric oxide, and 10 ml. of freshly distilled synthetic quinoline; it was then connected to the train. The air was swept out of the system with nitrogen, and the stopcock at the entrance to A was closed. A Dry Ice–isopropanol mixture was placed around the spiral trap and the temperature of the contents of A was raised from 150° to 265° over a period of one hour. The stopcock was then opened and a current of purified nitrogen was passed through the

[7] Unless sulfate is completely removed, the toluene obtained by decarboxylation of the uvitic acid contains sulfur dioxide.

apparatus for 3 hours, while the salt-bath was held at 265 ± 5°. The fore-trap was not cooled; it collected some water and toluene and most of the small amount of quinoline which distilled with them. This partial removal of extraneous substances reduced difficulty from plugs of frozen material in the coils of the spiral trap.

The spiral trap was watched closely and the cooling bath was removed for a brief time, if necessary, to allow plugs to melt and fall into the receptacle. Toward the end of the reaction, toluene in the fore-trap was driven into r by stroking the trap with a soft flame.

When the reaction was finished, barium carbonate was precipitated from the absorber solution. The yield was 7.45 g. after correction for blank (98.5%). This specimen is referred to in Table I as Barium Carbonate IV.

The toluene was purified with the aid of the apparatus shown in Fig. 3. This consists of a high vacuum manifold to which are attached vessels D, F and G. A trap H is situated in the line. The unit D contains the crude toluene; the entrance to the fore-trap is closed by a ground glass plug. Vessel F contains about 10 g. of phosphorus pentoxide, and G is a

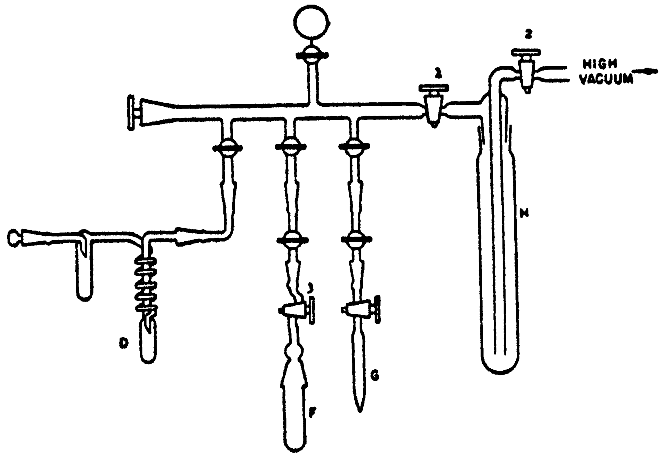

FIGURE 3. APPARATUS FOR THE PURIFICATION OF TOLUENE

receptacle made by sealing a 3-mm. straight bore stopcock to a 15-ml. graduated conical centrifuge tube. The stopcock and the ground joint by which the receptacle is attached to the manifold are sealed to the centrifuge tube on a lathe, to insure that all the segments are coaxial; it is then possible to insert a long capillary pipet into the tube to withdraw portions of toluene for use, and the receptacle can be used as a storage vessel.

The contents of the spiral trap were frozen in liquid nitrogen and the pressure in the entire system reduced to 5 microns; stopcock 1 was then closed. The toluene was transferred to F by cooling that vessel with liquid nitrogen while D was allowed to warm up. When most of the toluene had distilled, D was warmed in a bath of water at 40°. A pressure of 50 microns developed during the transfer as the materials in the system released entrained gases; toward the end of the operation these gases interfered with the diffusion of toluene. To obtain the last of the toluene, 1 was opened and the system reevacuated. The residual toluene condensed in H, which was cooled in liquid nitrogen. Stopcock 2 was then closed and the toluene in H was distilled into F.

Stopcock 3 was closed and F was removed from the line. By gently shaking the vessel, the phosphorus pentoxide and toluene were distributed in a layer over the entire inside wall area except the region near the stopcock. The vessel was again attached to the manifold and the toluene was distilled into G. A soft flame was passed a few times over F to drive out the last of the toluene.

The yield was 1.610 g.; 91.5% based on uvitic acid, or 62% based on pyruvic acid. The

purity of the product was investigated with a sample prepared in a pilot run with inactive pyruvic acid. The boiling range was 110.6–111.1°; n_D^{22} 1.4978. Mass spectrometric analysis[8] showed the total amount of impurities in the range of mass numbers 0 to 200 to be about 0.2%. Regions scanned with particular attention were those corresponding to benzene, xylene, methylcyclohexane and methylcyclohexene. The height of the toluene peak corresponded to 100.2 ± 0.2% toluene.

SUMMARY

1. A synthesis of toluene labeled with C^{14} in the 1, 3, and 5 positions of the ring is described. Labeled oxalic acid is obtained as a second product. The starting material is pyruvic acid-α-C^{14}; the yields of toluene and of sodium oxalate are 62% and 84%, respectively.

2. Certain aspects of the mechanisms of the reactions involved have been checked by tracer technique, with results consistent with concepts expressed in the literature.

3. The decarboxylation of methyldihydrotrimesic acid has been found to proceed by loss of the carboxyl carbon atom as carbon monoxide, not carbon dioxide. The formation of di- and tetra-hydrouvitic acids in this reaction is therefore questioned.

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[8] We wish to thank Dr. N. Bauer and the California Research Corporation for the mass spectrometric analysis.

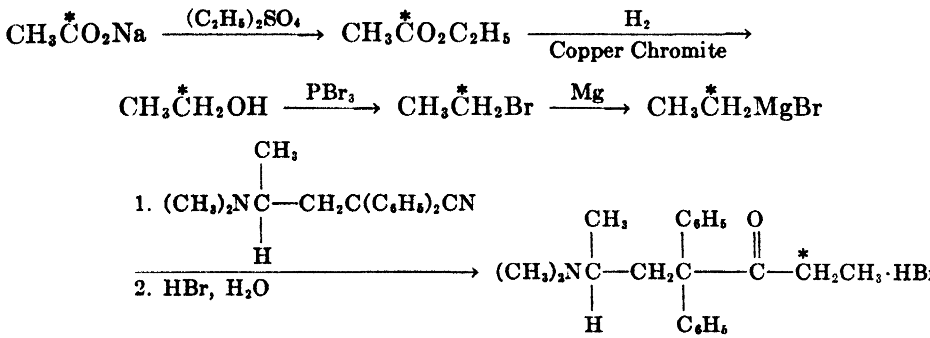
[CONTRIBUTION FROM THE RADIATION LABORATORY AND DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, AND DIVISION OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS AND COLLEGE OF PHARMACY, MEDICAL CENTER, UNIVERSITY OF CALIFORNIA]

SYNTHESIS OF ETHANOL-1-C[14], ETHANOL-2-C[14], ETHYL BROMIDE-1-C[14], ETHYL BROMIDE-2-C[14] AND C[14]-LABELED METHADONE[1]

B. M. TOLBERT, FREDA CHRISTENSON, FRANCES NAI-HSUAN CHANG, AND PETER P. T. SAH

Received December 27, 1948

In order to know more exactly how the analgesic methadone (4,4-diphenyl-6-dimethylamino-3-heptanone) (1, 2) acts in the animal body, we have prepared this compound with C[14] in the 2-position by the following series of reactions:



In a similar manner, 4,4-diphenyl-6-dimethylamino-3-heptanone-1-C[14] has been prepared using acetic acid-2-C[14] as the starting material.[2] The carboxyl- and methyl-labeled acetic acids were prepared by previously published procedures (3, 4, 5, 6).

The methadone-2-C[14] was prepared with a very high specific activity (0.5 μc/mg.), whereas the activity of the 1-labeled compound was only a few hundred counts/min/mg. In Table I the yields, specific activities, and scale of reactions are summarized for these two preparations. Animal studies on the *dl*-methadone-2-C[14] are in progress in the Division of Pharmacology, and the results will be published elsewhere.

EXPERIMENTAL

Preparation of labeled ethyl acetate. Labeled sodium acetate (0.7–1.0 g.) was dried *in vacuo* to about 1 μ pressure and weighed into a 30-ml. acetylation flask fitted with a 14/20 standard joint. Five ml. of redistilled diethyl sulfate was added to the flask, and a low temperature (Dry Ice) reflux condenser attached (see Fig. 1). The reaction mixture was heated on an oil-bath at 150–170° for 1–1.5 hours. The unit was then connected to the

[1] This paper is sponsored, in part, by the Atomic Energy Commission and, in part, by a grant from the National Institutes of Health.

[2] The nomenclature system for the labeled organic compounds is the same as that described in reference (4). For a similar scheme see Otvos and Wagner, *Science*, **106**, 409 (1947).

vacuum line (see Fig. 2) and the ethyl acetate distilled *in vacuo* from the diethyl sulfate. All but a trace of high-boiling impurities (mostly diethyl sulfate) were then removed by a second vacuum distillation. The yield of ethyl acetate by this method is 95–97% as deter-

TABLE I

PREPARATION OF METHADONE-2-C^{14}

	WEIGHT, GM.	M MOLE	SP. ACT. μC/MG	YIELD % BASED ON CO_2
$BaCO_3$	2.04	13.5	2.59	—
Sodium acetate-1-C^{14}	0.697	8.5	6.2	86[a]
Ethyl bromide-1-C^{14}	1.43	13.1	—	66.2
Methadone-2-C^{14}	1.00	2.56	0.55	9.5

[a] This yield was low; other radioactive runs have given yields of 91.3, 93.0, and 94.2%

PREPARATION OF METHADONE-1-C^{14}

	WEIGHT, GM.	M MOLE	SP. ACT. CTS/MIN/MG	YIELD % BASED ON CO_2
Sodium acetate-2-C^{14}	1.01	12.3	4.88×10^3	63.7
Ethyl bromide-2-C^{14}	2.05	18.8	—	46.0
Methadone-1-C^{14}	1.20[b]	3.22[b]	4.08×10^2	12.5

[b] Not all of the ethyl bromide was used in this condensation.

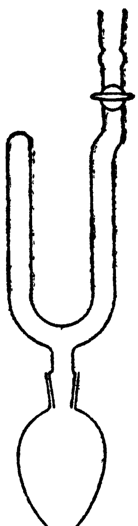


FIGURE 1

mined by saponification of the ester. A small amount of diethyl ether is present in the ethyl acetate.

Preparation of labeled ethanol. The ethyl acetate prepared as described was vacuum distilled into a 115 ml. hydrogenation bomb,[3] charged with 5 g. of copper chromite catalyst (7). When the distillation was completed, the bomb was closed, warmed to room

[3] American Instrument Company, Micro bomb, 180 ml. capacity.

temperature, filled with hydrogen to 2500 psi, and heated, with shaking, for 10 hours at 250°.

After the bomb had cooled to room temperature, it was reconnected to the vacuum line and the hydrogen removed by discharging the bomb contents through a liquid nitrogen-cooled spiral trap (see Fig. 2).

After the hydrogen was removed, the bomb was evacuated and the volatile contents of the bomb, as well as those in the warmed spiral trap, were vacuum distilled into the larger trap on the manifold. This product, a mixture of ethanol, water, and diethyl ether was treated without purification with phosphorus tribromide to prepare the halide.

To identify and isolate the ethanol, the mixture from a preliminary run was dried with calcium sulfate and distilled *in vacuo* into a micro distilling column pot. The ethanol was identified by its boiling point, 76–78°, and index of refraction, n_D^{17} 1.3624.

Preparation of ethyl bromide. The mixture of alcohol and water from the hydrogenation was distilled *in vacuo* into the bromination unit shown in Fig. 3. This unit was removed

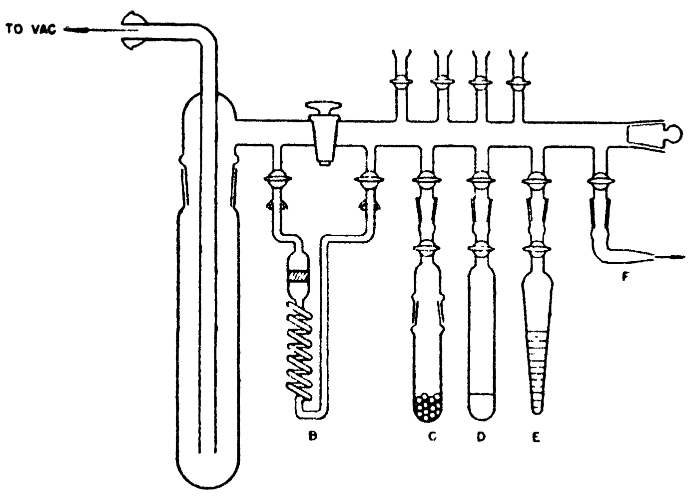


FIGURE 2

from the vacuum line and a second low-temperature condenser of the type shown in Fig. 1 connected to the ground joint. Both condensers were then cooled with Dry Ice-isopropyl alcohol, and phosphorus tribromide was added drop-wise to the alcohol-water mixture. A large excess of phosphorus tribromide (2–3 ml.) was added, and the mixture refluxed for 3 hours on a steam-bath. The entire bromination assembly was then connected to the vacuum line, and the ethyl bromide, together with some volatile impurities, distilled into the large trap on the manifold.

The product mixture was vacuum distilled into a reaction tube containing 10 ml. of 1 N sodium hydroxide solution (see Fig. 2-D). The vessel was removed from the line and shaken for several minutes to remove acid impurities. To dry the ethyl bromide it was then distilled *in vacuo* (together with some water) into a second reaction tube containing about 1 g. phosphorus pentoxide (Fig. 2-C). This mixture was also warmed to room temperature and shaken several minutes. The ethyl bromide was vacuum distilled into yet a third reaction vessel and shaken with 5 ml. of concentrated sulfuric acid for several minutes to remove ether and olefins. The purified ethyl bromide was distilled into a storage vessel (Fig. 2-E). The halide was identified on an inactive run by its boiling point, 34–39°, and its index of refraction, n_D^{18} 1.4326. The yield of ethyl bromide was 67–77% based on acetic acid.

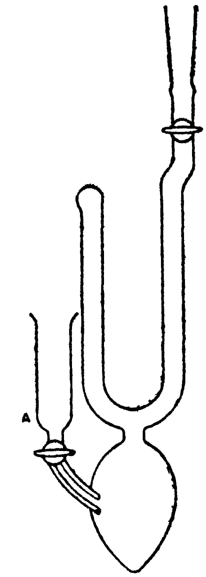


FIGURE 3

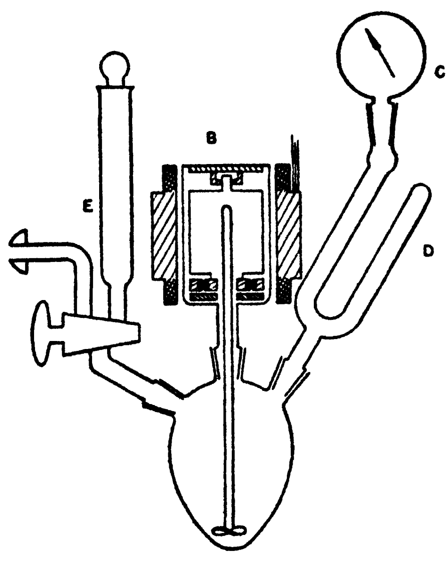


FIGURE 4

Purification of 2,2-diphenyl-4-dimethylaminopentanenitrile. The nitrile, donated by Eli Lilly and Company, was decolorized with Norit A and recrystallized three times from 80% ethanol. The product, consisting of large white prisms, was dried with calcium chloride *in vacuo*, m.p. 91–91.2°.

Anal. Calc'd for $C_{19}H_{22}N_2$: C, 81.97; H, 7.97; N, 10.06.

Found: C, 81.98, 81.97; H, 7.95, 7.80; N, 10.26, 10.28.

Preparation of the labeled ethyl Grignard and condensation with the nitrile. The ethyl

Grignard was prepared on the vacuum line and the nitrile added in benzene solution. The apparatus for the reaction is shown in Fig. 4. Nitrogen was admitted to the dried, well-evacuated system containing 0.35 g. of magnesium turnings. Ten ml. of dry ether was then pipetted into the reaction flask through the stirrer opening. After the stirrer was replaced, the ether was frozen in liquid nitrogen and the system was re-evacuated. Labeled ethyl bromide (approximately 1 ml.) was vacuum distilled into the flask which was then closed from the manifold. With an ice-acetone mixture in the condenser the ether solution was refluxed, with stirring, for 1 hour. Through the dropping-funnel was then added 2.35 g. of the nitrile dissolved in 6 ml. of dry benzene. The dropping-funnel was washed twice with 1 ml. of dry benzene; the benzene solution was added slowly enough that no air was drawn into the reaction vessel. The solution was then refluxed for 3 hours; a white precipitate formed. The Grignard flask was transferred to the hood, cooled to 0°, opened, and 24.4 ml. of 20% hydrobromic acid solution added drop-wise to decompose the Grignard complex.

Purification of the methadone. The impure methadone solution was transferred to an Erlenmeyer flask and heated on the steam-bath. After the ether and benzene were boiled off, the acid solution was cooled and extracted with ether. The water layer was made alkaline with 20 ml. of 3 *N* sodium hydroxide and extracted with ether. The ether extract from the alkaline solution was evaporated to a small volume, and 2 ml. of 20% hydrobromic acid was added. The acid solution was heated on a steam-bath again to expel ether. Then a few ml. of absolute ethanol was added. The ethanol solution was concentrated on the steam-bath, and the *methadone hydrobromide* crystallized out, filtered, and recrystallized from 80% ethanol. The absorption spectra and analgesic properties of the active and inactive samples of methadone produced were checked with samples prepared by Eli Lilly and Company and found to be the same, m.p. 224°.

Anal. Calc'd for $C_{21}H_{28}BrNO$: C, 64.61; H, 7.23.
Found: C, 65.23, 65.22; H, 7.27, 7.40.

Acknowledgment. The authors wish to thank Philip F. Kirk for his technical assistance in the Grignard reactions, Dr. Louis Strait for his aid in identifying and analyzing the methadone by absorption spectra measurements, Dr. H. W. Elliott for the determination of the analgesic potency of the sample, and the help and encouragement of Professors Hamilton H. Anderson, M. Calvin, and John F. Oneto.

SUMMARY

1. Semi-micro, high yield synthetic procedures have been developed for ethanol-1-C^{14}, ethanol-2-C^{14}, ethyl bromide-1-C^{14}, and ethyl bromide-2-C^{14}.

2. *dl*-Methadone (4,4-diphenyl-6-dimethylamino-3-heptanone) has been prepared labeled with C^{14} in either the 1 or 2 position.

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[Contribution from the William H. Nichols Laboratory, New York University]

STUDIES IN PIPERIDONE CHEMISTRY. I. A SYNTHESIS OF 5-HOMOPIPERAZINONES

S. C. DICKERMAN and H. G. LINDWALL

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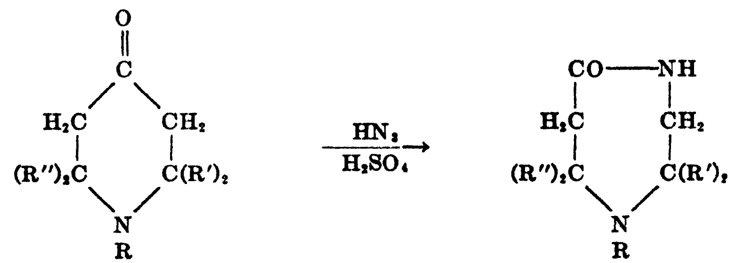
The extension of either the well-known Schmidt reaction (1) or the Beckmann rearrangement (2) to 4-piperidones or their oximes should result in the synthesis of 5-homopiperazinones.

Triacetonamine or 2,2,6,6-tetramethyl-4-piperidone (I) was prepared from phorone by the procedure described by Guareschi (3). When the amino ketone, I, was treated with hydrazoic and sulfuric acids, 2,2,7,7-tetramethyl-5-homopiperazinone (II) was formed in a yield of 88%. The following equation illustrates this and subsequent Schmidt reactions:



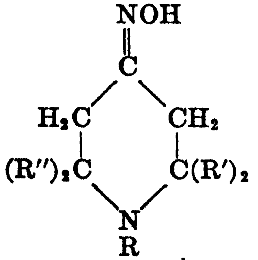
I. R = H, R′ = R″ = CH_3
VI. R = CH_3, R′ = R″ = H
XIII. R = R′ = R″ = H

II. R = H, R′ = R″ = CH_3
VII. R = CH_3, R′ = R″ = H
XVII. R = R′ = R″ = H

The cyclic amide, II, was hydrolyzed with dilute hydrochloric acid. The only product isolated was 1,2-diamino-2-methylpropane dihydrochloride (III). Therefore it would appear that cleavage of the amide linkage n II was accompanied by β-deamination. The diamine, III, was identified by cionversion to the diacetyl derivative and comparison with an authentic sample.

In order to further substantiate the homopiperazinone structure, the presence of a secondary amino group was demonstrated by converting the cyclic amide, II, to 1-nitroso-2,2,7,7-tetramethyl-5-homopiperazinone (IV). This neutral nitroso derivative, IV, gave a positive Liebermann test (4).

A Beckmann rearrangement of triacetonamine oxime (V) should afford another method of synthesis of the cyclic amide, II.



V. R = H, R′ = R″ = CH_3

VIII. R = CH_3, R′ = R″ = H

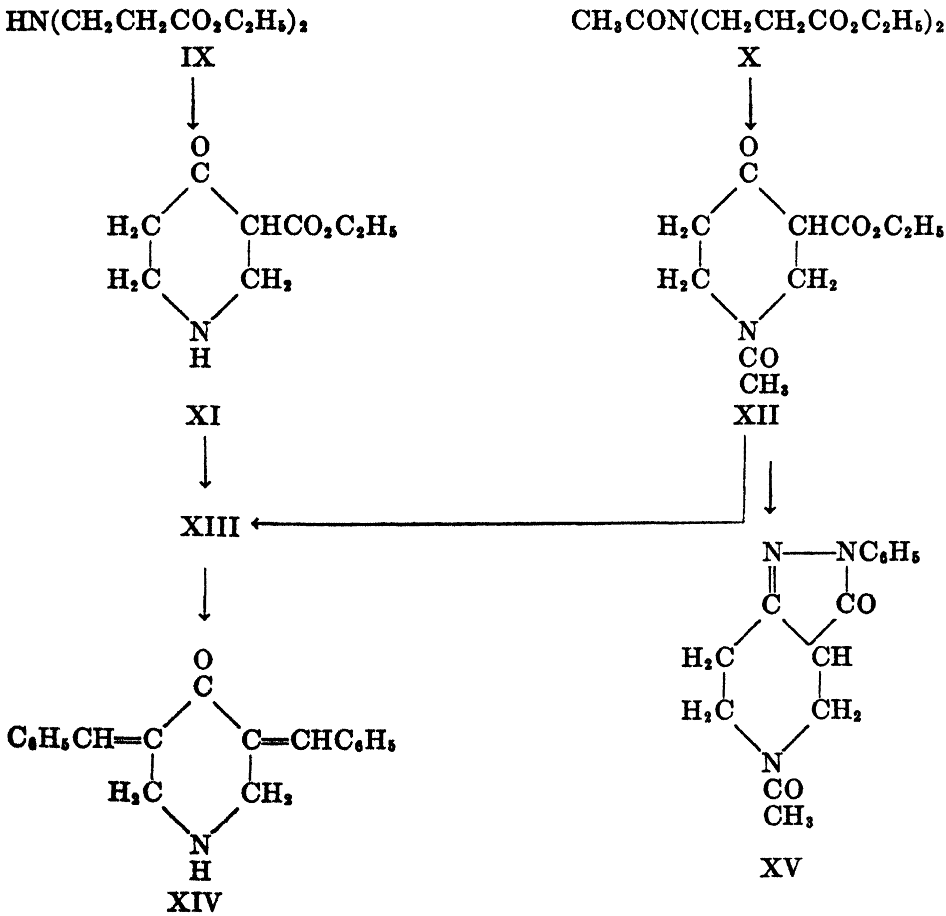
XVI. R = R′ = R″ = H

The common reagents for this rearrangement, phosphorus pentachloride and sulfuric acid, were tried unsuccessfully. However, thionyl chloride did bring about conversion of the oxime, V, to the amide, II, although in poor yield.

Since it seemed advisable to include an N-alkylamino ketone in this investigation, 1-methyl-4-piperidone (VI) was prepared by known (5, 6) methods. This ketone, VI, was readily converted to 1-methyl-5-homopiperazinone (VII) with hydrazoic and sulfuric acids in 53% yield.

The compounds, 1-methyl-4-piperidone oxime (VIII) and its hydrochloride were also prepared. These hitherto unreported compounds have some value as crystalline derivatives of the ketone, VI, but were synthesized with the hope that one would undergo a Beckmann rearrangement to the amide, VII. However, thionyl chloride and other acidic reagents produced only intractable red oils.

The last amino ketone selected for this investigation was 4-piperidone (XIII). Although this ketone, XIII, had been previously reported (8, 9, 10), certain difficulties and discrepancies were encountered in its synthesis. The accompanying diagram illustrates the method used by previous workers and the modification employed in this research.



The amino ester, di-(β-carbethoxyethyl)amine (IX) was synthesized from di(β-cyanoethyl)amine by a procedure outlined in the patent literature (7).

Ruzicka and co-workers (8, 9) first prepared 4-piperidone but were unable to isolate crystalline hydrochlorides of 3-carbethoxy-4-piperidone (XI) or 4-piperidone (XIII) nor could they distill either of these amines. They demonstrated the presence of 4-piperidone by preparing 3,5-dibenzal-4-piperidone hydrochloride (XIV). Some years later Kuettel and McElvain (10) isolated the keto ester, XI, as a crystalline hydrochloride and obtained two crystalline modifications of 4-piperidone hydrochloride. These hydrochlorides were assigned monohydrate and sesqui-ethanolate structures on the basis of ionic chloride determinations.[1]

The synthesis of Kuettel and McElvain (10) was repeated with the hope that the yield of 11% in the Dieckmann condensation could be improved. The ester, XI, was isolated but with no improvement in yield. Therefore the secondary amino group in the amino ester, IX, was blocked with an acetyl group. After N-acetyldi-(β-carbethoxyethyl)amine (X) had been synthesized in the course of this research, McElvain and Stork (11) reported the preparation of this compound. Furthermore, they reported that they attempted a Dieckmann condensation of the acetylated ester, X, but isolated only a trace of an oil which was not further investigated. This condensation was repeated with some changes in conditions and isolation procedure and 1-acetyl-3-carbethoxy-4-piperidone (XII) was isolated in 72% yield. The β-keto ester, XII, gave a vivid color with ferric chloride and formed a pyrazolone, XV, when heated with phenylhydrazine.

Hydrolysis of the acetamino-ester, XII, with dilute hydrochloric acid and crystallization from ethanol gave 4-piperidone hydrochloride sesqui-ethanolate as reported by Kuettel and McElvain (10).

The sesqui-ethanolate of 4-piperidone hydrochloride was converted to the monohydrate. After recrystallization, we found 4-piperidone hydrochloride monohydrate to melt from 140–145° with decomposition while Kuettel and McElvain (10) have reported a melting point of 92–94°. Because of this discrepancy in melting points, samples of 4-piperidone hydrochloride which had been prepared from the amino ester, XI, and the acetamino ester, XII, respectively, were converted to the known 3,5-dibenzal-4-piperidone hydrochloride (XIV) and the hitherto unknown derivative, 1-nitroso-4-piperidone (XV). Identical derivatives were obtained from both samples.

Further confirmatory evidence was obtained by the preparation of 4-piperidone oxime (XVI) and hydrochloride.

Finally, 4-piperidone hydrochloride monohydrate was converted to 5-homopiperazinone (XVII) with hydrazoic and sulfuric acids. One attempt to demonstrate the presence of a secondary amino group by the preparation of an N-nitroso derivative failed, and lack of material prevented repetition of the reac-

[1] (added in press) In a recent paper dealing with 4-piperidone and derivatives, McElvain and McMahon [*J. Am. Chem. Soc.* **71**, 901 (1949)] now formulate 4-piperidone hydrochloride sesqui-ethanolate as a diethyl ketal. We had considered this a likely possibility but our analyses did not indicate this structure.

tion. Therefore, the structure of compound XVII is formulated by analogy with previous Schmidt reaction products and should be regarded as tentative.

Further work on these compounds and other applications of the Schmidt reaction in this field are in progress in these laboratories.

EXPERIMENTAL[2, 3]

2,2,6,6-Tetramethyl-4-piperidone (I) was prepared by the method of Guareschi (3) from technical grade 42% phorone, which was used without purification, in a yield of 34%. Recrystallization from wet isopropyl ether gave the monohydrate of I; m.p. 58–60°.

2,2,7,7-Tetramethyl-5-homopiperazinone (II) was prepared by a Schmidt reaction as follows: A solution of 1.73 g. (0.01 mole) of 2,2,6,6-tetramethyl-4-piperidone monohydrate in 10 ml. of chloroform was dried over potassium carbonate, filtered into an eight-inch test tube, and cooled in an ice-bath. To this cold, vigorously stirred, solution was added dropwise 8 ml. of concentrated sulfuric acid. Sodium azide (1.62 g. = 0.025 mole) was then added in small portions, over a period of thirty minutes, through a small funnel of such shape that the solid dropped directly into the mixture. The stirring was continued for another fifteen minutes. The mixture was then diluted with 45 ml. of ice and water. This diluted solution was saturated with solid potassium carbonate and extracted with eight 50-ml. portions of ether. The combined ether extracts were dried over potassium carbonate, filtered, and brought, under reduced pressure, to dryness. The yield of almost white crude product amounted to 1.52 g. (88%); m.p. 140–145°. Recrystallization from dry benzene gave thick, white plates that melted at 147.5–148°.

Anal. Calc'd for $C_9H_{17}N_2O$: C, 63.5; H, 10.7; N, 16.5; Neut. equiv., 170.
Found: C, 63.1; H, 10.1; N, 16.3; Neut. equiv., 169.

The *hydrochloride* of I was prepared in absolute ethanol with alcoholic hydrogen chloride; recrystallized from ethanol; m.p. 295–300° with dec.

Anal. Calc'd for $C_9H_{19}ClN_2O$: N, 13.6. Found: N, 13.6, 13.4

Hydolysis of the amide, II was accomplished by refluxing in 20% hydrochloric acid for 40 hrs. Some unreacted amide, II, was recovered and the corrected yield of 1,2-diamino-2-methylpropane dihydrochloride (III) amounted to 71%; m.p. 290–300° with dec. [Mills and Quibell (12) reported 298–300° with dec.].

Anal. Calc'd for $C_4H_{14}Cl_2N_2$: N, 17.4. Found: N, 17.2.

The *diacetyl* derivative of III melted at 97–99°, while a mixture of this derivative and 1,2-diacetamino-2-methylpropane, prepared according to Drew and Head (13), melted at 97–99°. [They (13) reported a melting point of 100° for this compound.]

1-Nitroso-2,2,7,7-tetramethyl-5-homopiperazinone (IV) was prepared by heating a water solution of 108 mg. of II hydrochloride and 41 mg. of sodium nitrite on the steam-bath for an hour. The yellowish-green solution was adjusted to *p*H 2–4 with one drop of dilute hydrochloride acid, and extracted with several portions of ether. The combined ether extracts were brought to dryness and the residue recrystallized from a mixture of benzene and ligroin (70–90°). IV was obtained in 58% yield as pale yellow needles that melted at 150.5–151.0°. IV gave a positive Liebermann test (4).

Anal. Calc'd for $C_9H_{17}N_3O_2$: N, 21.1. Found: N, 21.0.

2,2,6,6-Tetramethyl-4-piperidone oxime (V) hydrochloride was prepared in 90% yield by refluxing an aqueous ethanol solution of the ketone, I, and hydroxylamine hydrochloride; white plates; m.p. about 300° with dec.

Anal. Calc'd for $C_9H_{19}ClN_2O$: Cl, 17.2: N, 13.6. Found Cl, 17.0; N, 13.7.

2,2,7,7-Tetramethyl-5-homopiperazinone (II) was prepared by a Beckmann rearrangement as follows: 1.00 g. of the hydrochloride of II was dissolved in 10 ml. of cold, freshly

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[2] All melting points are corrected; boiling points are uncorrected.

[3] The authors wish to thank E. J. Moriconi and A. J. Besozzi for performing some of the microanalyses.

distilled, thionyl chloride. The initially colorless solution turned yellow and gradually deposited a red oil. After standing for 14 hrs. at room temp., the excess thionyl chloride was removed under reduced pressure. The dark red oil that remained was dissolved in 5 ml. of ice-water, decolorized with Norit and again brought to dryness under reduced pressure to yield a red oil that crystallized when triturated with absolute ethanol. This crude hycrochloride was converted to the free base with aqueous potassium carbonate and extracted with benzene. The residue obtained by the evaporation of the combined benzene extracts was recrystallized six times from isopropyl ether. II was obtained as white plates that melted at 144.5–146.0°. The mixed melting point with the oxime, V, was 110–125° and with the amide, II, prepared by the Schmidt reaction, 146–147°.

1-Methyl-5-homopiperazinone (*VII*) was prepared by a procedure analogous to that used for II; however, chloroform was used to extract VII from the saturated potassium carbonate solution. From 1.50 g. (0.010 mole) of 1-methyl-4-piperidone hydrochloride, prepared by known methods (5, 6), and 0.78 g. (0.012 mole) of sodium azide, VII was obtained in 53% yield; recrystallized from petroleum ether (30–60°) as hygroscopic white needles of m.p. 83–84°.

Anal. Calc'd for $C_6H_{12}N_2O$: N, 21.9; Neut. equiv., 128.
Found: N, 21.6; Neut. equiv., 129.

The *hydrochloride* of VII was prepared in absolute ethanol with alcoholic hydrogen chloride; recrystallized from ethanol was a white, hygroscopic, microcrystalline solid; m.p. 209–210°.

Anal. Calc'd for $C_6H_{13}ClN_2O$: Cl, 21.6. Found: Cl, 21.6.

1-Methyl-4-piperidone oxime (*VIII*) *hydrochloride* was prepared in 85% yield by refluxing an aqueous ethanol solution of the ketone, VI, (b.p. 51.0–52.5° at 8 mm.) [43.5–44.1° at 6 mm. and 56–58° at 8 mm. have been reported (6, 14)] and hydroxylamine hydrochloride; white needles, m.p. 243–244° with dec.

Anal. Calc'd for $C_6H_{13}ClN_2O$: N, 17.0. Found: N, 16.8.

The hydrochloride was converted to the amine, VIII, with ethereal ammonia; recrystallized from dry benzene. *1-Methyl-4-piperidone oxime* (*VIII*) was obtained as white needles, m.p. 129.5–130.0°.

Anal. Calc'd for $C_6H_{12}N_2O$: N, 21.9; Neut. equiv., 128.
Found: N, 21.6; Neut. equiv., 127.

Di-(β-carbethoxyethyl)amine (*IX*) was prepared by the method outlined in the patent literature (7) and a procedure adapted from Organic Syntheses (15) for a similar reaction. Di-(β-cyanoethyl)amine, 24.6 g. (0.20 mole) was converted to 28.0 g. (64%) of IX; b.p. 108–110° at 0.1 mm. [The b.p. of IX, prepared by another method has been reported (11) as 119–125° at 1–2 mm.]

1-Acetyl-3-carbethoxy-4-piperidone (*XI*) was prepared from N-acetyldi-(β-carbethoxyethyl)amine; b.p. 151–155° at 0.1 mm.; n_D^{27} 1.4612. [McElvain and Stork (11) reported b.p. 183–185° at 5 mm.] To a suspension of 4.6 g. (0.2 g. atom) of sodium-sand in 200 ml. of dry xylene was added 51.8 g. (0.2 mole) of X and 0.5 ml. of absolute ethanol. The mixture was then stirred and heated until the xylene just began to reflux when a vigorous reaction, that required cooling, took place and the reaction product separated as a yellow solid. After the initial reaction had subsided, the mixture was heated and stirred for another hour. After cooling, the solid was filtered off and washed with several portions of petroleum ether. The yield of crude sodium salt amounted to 42.0 g. A solution of 23.5 g. of this sodium salt in 35 ml. of water was extracted with two 25-ml. portions of chloroform, cooled in an ice-bath and acidified with conc'd hydrochloric acid. This acidic solution was saturated with sodium chloride and extracted with seven 25-ml. portions of chloroform. The combined extracts were dried over magnesium sulfate, filtered, and brought under reduced pressure to a pale yellow oil that crystallized on standing overnight to waxy needles; yield 17.3 g., or 72% from X. The keto-ester melted from 30–40° and could not be distilled under oil-pump vacuum; nor could it be recrystallized. It gave a vivid reddish-purple color with 10% ferric chloride. It was vacuum dried over phosphorus pentoxide before analysis.

Anal. Calc'd for $C_{10}H_{15}NO_4$: C, 56.3; H, 7.1.
Found: C, 56.1; H, 7.0.

6-Acetylpiperidino(4',3'-c)-2-phenyl-3-pyrazolone (XIII) was prepared as follows: 1-acetyl-3-carbethoxy-4-piperidone (XI) (0.483 g.) and phenylhydrazine (0.269 g.) were dissolved in 10 ml. of 50% ethanol, and the solution heated on a steam-bath for six hours. The viscous yellow oil, that remained, crystallized on standing overnight. The product was washed with ether and recrystallized from ethanol. The yield of XIII amounted to 84%; the microcrystalline, white powder melted at 191–192° with dec.

Anal. Calc'd for $C_{14}H_{15}N_3O_2$: C, 65.3; H, 5.9; N, 16.3.
Found: C, 65.2; H, 6.0; N, 16.4.

4-Piperidone (XIII) hydrochloride was prepared by two methods as follows:

(a) 3-Carbethoxy-4-piperidone (XI) hydrochloride was synthesized and converted to XIII as described by Kuettel and McElvain (10). 4-Piperidone hydrochloride sesqui-ethanolate was isolated in 67% yield; m.p. 120–130° with dec. [K. and M. (10) reported a yield of 48% of material melting at 139–140° with dec.]

(b) 1-Acetyl-3-carbethoxy-4-piperidone (XI) (16.3 g.) was refluxed for seven hours with 250 ml. of 6 *N* hydrochloric acid. After decolorizing with 0.5 g. of Norit, the solution was filtered and evaporated under reduced pressure to a syrup that crystallized when triturated with absolute ethanol; recrystallized from absolute ethanol and ether. The yield of white needles of 4-piperidone hydrochloride sesqui-ethanolate amounted to 9.0 g. (58%); m.p. 120–130° with dec. After two more recrystallizations it melted at 136–138° with dec. [K. and M. (10) reported 139–141° with dec.]

Anal. Calc'd for $C_5H_9NO \cdot HCl \cdot C_2H_5OH$: C, 46.3; H, 9.9; Cl, 19.5; N, 7.7.
Calc'd for $C_5H_9NO \cdot HCl \cdot 1.5\ C_2H_5OH$; C, 47.0; H, 9.4; Cl 17.3; N, 6.8.
Found: C, 46.7, 46.8; H, 9.3, 9.6; Cl, 17.5; N, 6.8.

4-Piperidone hydrochloride sesqui-ethanolate was converted to the hydrate by refluxing with 5% hydrochloric acid for thirty minutes followed by removal of the water and acid under reduced pressure. 4-Piperidone hydrochloride monohydrate was isolated as white granules of m.p. 140–145° with dec. After recrystallization from a mixture of acetone and water, the hydrate was obtained as transparent nuggets that again melted at 140–145° with dec. [K. and M. (10) have reported a melting point of 92–94°.]

Anal. Calc'd for $C_5H_9NO \cdot HCl \cdot H_2O$: C, 39.1; H, 7.9; Cl, 23.0; N, 9.1.
Found: C, 39.3; H, 7.8; Cl, 23.1; N, 9.0.

3,5-Dibenzal-4-piperidone hydrochloride (XIV) was prepared as described by Kuettel and McElvain (10) from two samples of the sequi-ethanolate obtained from XI and XII. Both preparations of the dibenzal derivative were obtained as yellow needles that melted separately or mixed from 250–278° with some dec. from 250–270° and vigorous dec. from 270–278°. The decomposition point was taken by placing the sample on the cold block and raising the temp. as rapidly as possible to 230°, then at a rate of 5° per minute [other reported decomposition points are 275–277° (8) and 276–277° (10)].

Anal. Calc'd for $C_{19}H_{18}ClNO$: Cl, 11.4; N, 4.5.
Found: Cl, 11.3, N, 4.6.

1-Nitroso-4-piperidone (XV) was prepared from the two samples of 4-piperidone hydrochloride sesqui-ethanolate obtained from XI and XII by the procedure use for IV. The yield, in both cases, of pale yellow needles of m.p. 61–62° amounted to 60%; mixed m.p. 61–62°. Both samples of this nitrosamine gave a positive Liebermann test (4).

Anal. Calc'd for $C_5H_8N_2O_2$: N, 21.9. Found: N, 22.1.

4-Piperidone oxime (XVI) was prepared as follows: 4-piperidone hydrochloride monohydrate (0.250 g.), hydroxylamine hydrochloride (0.136 g.), and sodium bicarbonate (0.165 g.) were dissolved in 2 ml. of water. After standing overnight, the solution was saturated with anhydrous potassium carbonate and extracted with five 5-ml. portions of chloroform. The combined extracts were dried over potassium carbonate and brought to dryness under reduced pressure. The yield of crystalline crude product amounted to 0.139 g. (75%); recrystallized from dry benzene to yield white, somewhat hygroscopic needles, m.p. 117–118°.

Anal. Calc'd for $C_5H_{10}N_2O$: N, 24.5; Neut. equiv., 114.
Found: N, 24.7; Neut. equiv., 113.

A portion of XVI in absolute ethanol was converted to the hydrochloride with ethanolic hydrogen chloride. The product crystallized from absolute ethanol as long, silky needles, m.p. 233–235° with dec.

Anal. Calc'd for $C_5H_{11}ClN_2O$: Cl, 23.5. Found: Cl, 23.4.

5-Homopiperazinone (*XVII*) was prepared from 0.515 g. of 4-piperidone hydrochloride monohydrate by a procedure analogous to that used for the preparation of II. Removal of the ether yielded a red oil that showed no tendency toward crystallization and was, therefore, converted to the hydrochloride with ethanolic hydrogen chloride. After crystallization from ethanol, 0.269 g. (51%) of *XVII hydrochloride* was obtained as white, hygroscopic needles, m.p. *223–225°*.

Anal. Calc'd for $C_5H_{11}ClN_2O$: C, 39.9; H, 7.4, N, 18.6.
Found: C, 40.0; H, 7.3; N, 18.6.

SUMMARY

1. The Schmidt reaction has been extended to three piperidones, 2,2,6,6-tetramethyl-4-piperidone, 1-methyl-4-piperidone, and 4-piperidone.

2. At least two homopiperazinones have been isolated and characterized.

3. Contrary to a literature report, N-acetyl-di-(β-carbethoxyethyl)amine has been found to undergo a Dieckmann condensation.

4. A literature method of synthesis of 4-piperidone has been modified with some improvement in yield.

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[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY, UNIVERSITY OF CHICAGO]

REACTIONS OF ATOMS AND FREE RADICALS IN SOLUTION. XXI. THE RELATIVE REACTIVITY OF OLEFINS TOWARDS A FREE TRICHLOROMETHYL RADICAL

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It has been postulated in previous articles from this Laboratory that the addition to olefins of polyhalomethanes (1), α-bromo esters, etc. (2), proceeds in two steps. Specifically, the addition of bromotrichloromethane to olefins in the presence of light is assumed to proceed as follows:

$$BrCCl_3 \xrightarrow{h\nu} \cdot Br + Cl_3C\cdot$$

1. $RCH{=}CH_2 + Cl_3C\cdot \rightarrow \cdot CHRCH_2CCl_3$
2. $\cdot CHRCH_2CCl_3 + Cl_3CBr \rightarrow RCHBrCH_2CCl_3 + Cl_3C\cdot$

The energetics of the two steps are different for the same olefin, and, furthermore, the energetics for the same step differ from olefin to olefin. In the present paper the relative reactivities of a number of olefins, as regards their respective abilities to react with free trichloromethyl radicals (Step 1) have been evaluated.

It is obvious that in order to compare olefins with regard to Step 1 the experimental conditions must be carefully adjusted to insure that Step 2 takes place readily. In the present study this has been accomplished by using bromotrichloromethane as the reagent, since at 50–60° it reacts with all the olefins used in this study to give excellent yields of the one-to-one adducts.

RESULTS

Before a comparison of the reactivities of the olefins was undertaken, the one-to-one adducts of bromotrichloromethane and the olefins were prepared and carefully characterized (Table II). Whenever possible, pairs of olefins which gave adducts with bromotrichloromethane markedly different in boiling points and indices of refraction, were selected for comparison. Furthermore, whenever a mixture of two adducts was obtained, the composition of the reaction mixture was determined by: (a) analyses, (b) index of refraction. Since, in most cases the index of refraction is not a linear function of composition, it was necessary to construct index of refraction–molar composition curves from mixtures of the one-to-one adducts of known composition. In all cases, the compositions of the unknown mixtures determined from the index of refraction agreed very well with the values calculated from analyses for one or more elements.

In most of the experiments equimolecular mixtures of the two olefins were dissolved in four molecular equivalents of bromotrichloromethane, and the reaction mixture was irradiated by a mercury vapor-argon fluorescent coil (3). The progress of the reaction was followed by withdrawal of small samples and titration for unsaturates by a standard procedure. Ordinarily, the reaction was allowed to proceed until about 25–50% of the total olefins had reacted. In the case of

styrene and butadiene, which are tremendously more reactive than the ordinary olefins the reaction was carried to the point at which these olefins reacted almost completely.

The relative reactivity of a number of olefins toward the free trichloromethyl radical is indicated in Table I.

The structural characteristics of the olefins which increase or decrease the ability of the olefin to combine with a free trichloromethyl radical (Step 1) are, for the most part, self evident; what is of considerable interest is the very low reactivity of cyclohexene, β-methylstyrene, and ethyl cinnamate.

TABLE I

THE RELATIVE REACTIVITIES OF OLEFINS TOWARDS A FREE TRICHLOROMETHYL RADICAL

Styrene	>100.
Butadiene	18.0[a]
Methallyl chloride	1.6
2-Ethyl-1-butene	1.4
β-Methylstyrene	1.1
1-Octene	1.0
2-Methyl-2-butene	0.9
Ethyl cinnamate	.8
Vinyl acetate	.8
Ethyl vinylacetate	.7
Allylbenzene	.7
Allyl chloride	.5
Allyl cyanide	.3
4,4,4-Trichloro-1-butene	.3
Cyclohexene	.2

[a] Bromotrichloromethane adds to butadiene to give about 75 ± 10% of the 1,4 adduct and about 25 ± 10% of the 1,2 adduct (unpublished work of Kharasch and Nudenberg).

Structure of adducts of bromotrichloromethane with β-methylstyrene and with ethyl cinnamate. Only one of two possible structural isomers is formed by the addition of bromotrichloromethane to β-methylstyrene and to ethyl cinnamate.

$$C_6H_5CH{=}CHCH_3 + BrCCl_3 \rightarrow \underset{(I)}{C_6H_5CHBrCH(CH_3)CCl_3}$$

$$C_6H_5CH{=}CHCOOC_2H_5 + BrCCl_3 \rightarrow \underset{(II)}{C_6H_5CHBrCH(COOC_2H_5)CCl_3}$$

The structure of Compound I was established by hydrolysis (in glacial acetic acid containing hydrogen bromide) to α-methylcinnamic acid. Compound II when hydrolyzed in a similar way gave some cinnamic acid, and a large quantity of benzaldehyde. The formation of these products is to be expected if Compound II is first hydrolyzed to benzylidenemalonic acid (4).

EXPERIMENTAL

All of the experiments described in this paper were carried out in an atmosphere of nitrogen gas.

METHODS OF INITIATING THE REACTION OF BROMOTRICHLOROMETHANE WITH OLEFINS

(*a*) *Diacyl peroxide induced reactions.* The reactions, when initiated by the thermal decomposition of diacyl peroxides, were carried out in a three-necked flask of suitable capacity equipped with an all-glass stirrer, a dropping-funnel, and a suitable condenser. Ground-glass connections were used throughout. When low-boiling solvents were used a Dry Ice condenser was used to prevent loss of material. The condenser was attached to a long tube filled with calcium chloride.

(*b*) *Photochemically induced reactions.* Whenever the reactions were initiated photochemically, the reaction mixture was illuminated internally by a mercury vapor-argon fluorescent coil. Stirring was accomplished by passing a slow stream of nitrogen gas through a fine sintered disc in the bottom of the tube. The outlet and condenser system were arranged in the manner described in (*a*). Some reactions were carried out in containers from which the air was removed by the usual vacuum technique, and illuminated by a Mazda lamp.

ISOLATION OF REACTION PRODUCTS

In all of the experiments, the reaction mixture was worked up by removal of the unreacted bromotrichloromethane and olefin through a Vigreux column at about 50–100 mm., with the temperature of the heating bath below 70°. A very slow stream of nitrogen gas was admitted through a fine capillary tube to prevent superheating of the material.

The residue was usually fractionally distilled through a Vigreux column at 0.5 to 0.02 mm. pressure. A slow stream of nitrogen gas was admitted through a fine capillary tube. Any volatile materials were caught in a trap cooled with Dry Ice or in liquid nitrogen.

The preparation of 1-bromo-2-trichloromethylcyclohexane. The preparation of the adducts of bromotrichloromethane with the olefin given in Table II resembles in all of the essential details the preparation of 1-bromo-2-trichloromethylcyclohexane. Because this substance is thermally unstable, it was necessary to distill it at a low pressure and to avoid the use of a column.

A solution of 51.4 g. (0.63 mole) of peroxide free cyclohexene and 250 cc. (2.50 moles) of freshly distilled bromotrichloromethane was internally illuminated for 36 hours by a mercury vapor-argon fluorescent coil. The temperature of the mixture was maintained at 25° by external cooling. The unreacted materials were stripped through a Vigreux column at 30°/30 mm., and the temperature of the oil bath gradually raised to 55°, while a slow stream of nitrogen gas was admitted through a fine capillary tube. The residue (133 g.) was distilled through a short Claissen head and the following fractions were collected: Fraction I: 24 g., b.p. 35–83°/0.2 mm. This material fumed strongly in air and turned dark brown upon exposure to air. Fraction II: 53 g., b.p. 83–85°/0.3 mm. Very light yellow color; n_D^{20} 1.5470.

Anal. Fraction II. Calc'd for $C_7H_{10}Cl_3Br$: Ag equiv., 70.1; Mol. wt., 280.
Found: Ag equiv., 70.8; Mol. wt., 288.

The competitive addition of bromotrichloromethane to olefins. The apparatus used in the photochemical competition experiments was the same as that used in the initial preparations of the adducts of bromotrichloromethane to olefins, except that a graduated one-cc. pipet was sealed to the apparatus which enabled us to remove a definite amount of the reaction mixture. For details of the design of the apparatus the paper by Kharasch and Friedlander (3) should be consulted.

The two unsaturates in equimolar quantities were dissolved in a four-fold excess of bromotrichloromethane and duplicate one-cc. samples analyzed for unsaturation by the following procedure:

The sample (containing about 4 milliequiv. of the olefins) was added to 15 ml. of reagent grade carbon tetrachloride contained in a 100-ml. ground-glass stoppered container. A solution of 25 ml. of bromate-bromide (5 milliequiv. Br), and 3 ml. of concentrated HCl were then added, the vessel stoppered and shaken vigorously for about 30 seconds, and set

TABLE III

THE ADDITION OF BROMOTRICHLOROMETHANE TO OLEFINS[a]

OLEFIN	(MOLE)	MOLES $BrCCl_3$	TIME (HRS)	TEMP. (°C.)	PRODUCT	YIELD (%)	B.P./MM. (°C.)	n_D^{25}	AG EQUIV. Calc'd	AG EQUIV. Found	MOL. WT. Calc'd	MOL. WT. Found
$H_2C{=}CClCH_2Cl$	(0.1)	0.8	312	55	$Cl_3CCH_2CClBrCH_2Cl$[b]	8	52/0.03	1.5443	51.6	52.0	310	311
$H_2C{=}CHCH_2CN$	(.2)	0.8	14	30	$Cl_3CCH_2CHBrCH_2CN$[c]	65	77–78/0.03	1.5276	—	—	266	267
$H_2C{=}C(CH_3)CH_2Cl$	(.2)	1.0	4	40	$Cl_3CCH_2CBr(CH_3)CH_2Cl$	45	65/0.10	1.5341	57.6	57.3	—	—
$H_2C{=}CHCH_2CO_2C_2H_5$	(.2)	0.8	20	25	$Cl_3CCH_2CHBrCH_2CO_2C_2H_5$	92	73/0.06	1.4996	78.1	77.5	312	313
$H_2C{=}CHC_6H_3$-2,4-Cl_2	(.3)	1.0	6	50	$Cl_3CCH_2CHBrC_6H_3$-2,4-Cl_2	20	108/1.00	1.5973	61.9	62.1	371	344
$H_2C{=}CHCH_2C_6H_5$	(.2)	0.8	26	35	$Cl_3CCH_2CHBrCH_2C_6H_5$	49	79/0.05	1.5650	79.1	79.1	316	316
$H_2C{=}C(C_2H_5)_2$	(.2)	0.7	15	25	$Cl_2CCH_2CBr(C_2H_5)_2$	91	68/0.70	1.5156	70.5	70.2	283	288
$H_3CCH{=}C(CH_3)_2$	(.2)	0.8	34	50	$Cl_3CCH(CH_3)CBr(CH_3)_2$	77	32/0.07	1.5234	67.1	67.2	269	271
Cyclohexene	(.6)	2.5	36	25	1-Bromo-2-trichloromethyl cyclohexane	30	83–85/0.20	1.5470	70.1	70.8	281	285
$C_6H_5CH{=}CHCOOC_2H_5$	(.3)	1.0	3 days	75	$C_6H_5CHBrCH(COOC_2H_5)$-CCl_3[d]	60	M.P. 64.5	[e]	93.6	93.9	374	370

[a] Unless otherwise specified the reaction mixture was illuminated internally by a mercury vapor-argon fluorescent coil.

[b] Besides this product an equal quantity of an adduct of two molecules of the olefin and one molecule of bromotrichloromethane is formed. The addition of the reagent to the olefin takes place very slowly.

[c] *Anal.* Calc'd for $C_5H_5BrCl_3N$: N, 5.27%. Found: N, 5.26%.

[d] About four grams of diacetyl peroxide was added in 0.1 g. portions every four hours.

[e] Calc'd for $C_{12}H_{12}BrCl_3O_2$: C, 38.45; H, 3.20. Found: C, 38.53; H, 3.27.

TABLE III

COMPETITIVE PHOTOCHEMICAL REACTIONS OF OLEFINS WITH BROMOTRICHLOROMETHANE

REACTION NO.	OLEFIN A	(MOLE)	OLEFIN B	(MOLE)	MOLES $BrCCl_3$	TEMP. (°C)	TIME (MIN.)	PER CENT REACTION[a]	PER CENT A ADDUCT[b]
1	$H_2C{=}CH\text{-}n\text{-}C_6H_{13}$	(0.25)	$H_2C{=}CHCH_2Cl$	(0.25)	2.0	30	290	45	64.7 (I, Ag)
2[c, e]	$H_2C{=}CH\text{-}n\text{-}C_6H_{13}$	(.25)	$H_2C{=}CHC_6H_5$	(.25)	2.0	70	150	27	<1.0
3	$H_2C{=}CH\text{-}n\text{-}C_6H_{13}$	(.25)	$H_2C{=}C(CH_3)CH_2Cl$	(.25)	2.0	30	270	26	36.3 (I, Ag)
4	$H_2C{=}CH\text{-}n\text{-}C_6H_{13}$	(.25)	$H_2C{=}C(C_2H_5)_2$	(.25)	2.0	35	600	45	41.3 (I, Ag)
5	$H_2C{=}CH\text{-}n\text{-}C_6H_{13}$	(.25)	$H_2C{=}CHCH_2CN$	(.25)	2.0	35	1130	29	76.9 (I, N)
6[d, e]	$H_2C{=}CH\text{-}n\text{-}C_6H_{13}$	(.20)	$H_2C{=}CHCH{=}CH_2$	(.20)	0.2	68	840	—	5.6 (C, H)
7	$H_2C{=}CH\text{-}n\text{-}C_6H_{13}$	(.25)	$H_3CCH{=}C(CH_3)_2$	(.25)	2.0	30	180	39	53.0 (I, Ag)
8	$H_2C{=}CH\text{-}n\text{-}C_6H_{13}$	(.25)	$H_2C{=}CHCH_2CO_2C_2H_5$	(.25)	2.0	30	180	25	58.6 (C, H)
9	$H_2C{=}CH\text{-}n\text{-}C_6H_{13}$	(.25)	$H_2C{=}CHO_2CCH_3$	(.25)	2.0	30	180	49	55.5 (C, H)
10	$H_2C{=}CH\text{-}n\text{-}C_6H_{13}$	(.06)	$H_2C{=}CHCH_2CCl_3$	(.06)	0.24	45	100	45	66.0 (I)
11[d]	$H_2C{=}CHCH_2Cl$	(.25)	Cyclohexene	(.25)	0.25	25	1.6×10^4	—	73.7 (I, Ag)
12[c, e]	$H_2C{=}CHCH_2Cl$	(.19)	$H_2C{=}CHC_6H_5$	(.26)	2.0	70	180	28	<1.0
13	$H_2C{=}CH\text{-}n\text{-}C_6H_{13}$	(.10)	$H_2C{=}CH{-}CH_2C_6H_5$	(.10)	0.10	60	1680	37	60.0 (I)
14	$H_2C{=}CH\text{-}n\text{-}C_6H_{13}$	(.10)	$H_3CCH{=}CHC_6H_5$	(.10)	0.15	60	3600	—	47.0 (I)
15	$H_2C{=}CH\text{-}n\text{-}C_6H_{13}$	(.10)	$C_6H_5CH{=}CHCO_2C_2H_5$	(.10)	0.80	75	390	40	55.1 (I, Ag)

[a] In all cases in which bromotrichloromethane was present in material excess of the amount necessary to react with all the olefin present the total reaction percentage was regarded as equal to the percentage decrease in unsaturation as estimated by bromate-bromide titration.

[b] The percentage of one-to-one addition product that resulted from addition to olefin A was estimated in various ways: by determination of the index of refraction (I); by determination of the silver equivalent (Ag); by analyses for carbon (C), hydrogen (H), and nitrogen (N). The nature of the data on which the estimate is based is indicated by the appropriate symbol or symbols. When more than one symbol appears the figure reported is the average of closely concordant estimates.

[c] In reactions 2 and 12 the residue which remained after distillation solidified. The crude solid melted at 45–50°, indicating that it consisted substantially of the styrene (B) adduct (m.p., 54.5–55.0°).

[d] Reactions 6 and 11 were carried out in sealed containers.

[e] Reactions 2, 6, 12, and 15 were peroxide-induced, rather than photochemical; hence the relatively high temperatures at which they were conducted. Essentially the same results were obtained when reaction 1 was peroxide induced rather than photochemical.

aside in the dark place. After 15 minutes 1.0 g. of solid potassium iodide was quickly added and the bottle immediately restoppered and shaken vigorously. The iodine was then titrated with 0.1 *N* thiosulfate. To achieve greater accuracy in the titrations, it is desirable to replace the air in the flask by either carbon dioxide or nitrogen, and to allow the reaction mixture to stand four hours, instead of 30 seconds before adding the potassium iodide.

After the initial unsaturation per ml. had been determined, the reaction was allowed to proceed until 25–50% of the olefins had reacted. This usually required about 1–2 hours. At the end of that time, the reaction mixture was worked up in the manner previously described.

SUMMARY

1. The one-to-one adducts of the following olefins with bromotrichloromethane have been prepared: 2,3-dichloropropene-1, allyl cyanide, methallyl chloride, ethyl vinylacetate, allylbenzene, 2-ethyl-1-butene, 2-methyl-2-butene, ethyl cinnamate, and cyclohexene.

2. The relative reactivities of fifteen olefins towards a free trichloromethyl radical have been established.

CHICAGO 37, ILLINOIS

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[CONTRIBUTION No. 168 FROM THE RESEARCH LABORATORIES OF HOFFMANN-LA ROCHE, INC.]

THE REACTION OF ACETOPHENONE WITH FORMALDEHYDE AND METHYLAMINE HYDROCHLORIDE

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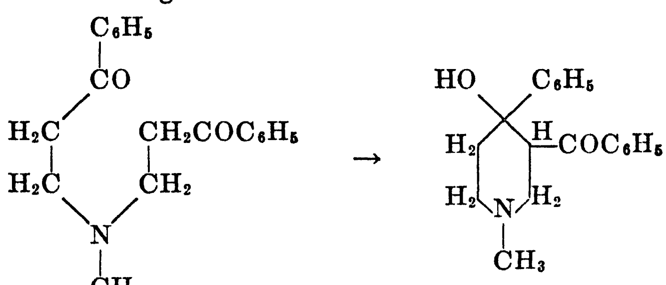
Mannich and Heilner (1) were the first to investigate the reaction of acetophenone, formaldehyde, and methylamine hydrochloride. They found that these reagents reacted readily in alcoholic solution, according to the following equations:

$$\text{(A)}\quad C_6H_5COCH_3 + CH_2O + CH_3NH_2\cdot HCl \rightarrow \underset{\text{I}}{C_6H_5COCH_2CH_2NHCH_3\cdot HCl}$$

$$\text{(B)}\quad 2C_6H_5COCH_3 + 2CH_2O + CH_3NH_2\cdot HCl \rightarrow \underset{\text{II}}{(C_6H_5COCH_2CH_2)_2NCH_3\cdot HCl}$$

A yield of 31% of bis-(β-benzoylethyl)methylamine hydrochloride (II) and an undetermined amount of I were obtained when the reagents were mixed in the proportions shown in equation B. When the reagents were mixed in equimolar quantities in the sense of equation A, Blicke and Burckhalter (2) obtained a 34% yield of I and a 29% yield of II.

Warnat (3) repeated the work of Mannich and Heilner but reported an additional compound (III),[1] whose formation he explained as an isomerization of II, according to the following scheme.



Base II III

Several years later Mannich and Hieronimus (5) confirmed the isolation of compound III without giving experimental details.

Apparently both Mannich and Warnat regard compound III as a component of the reaction mixture obtained after refluxing the alcoholic solution of the three reagents. It will be subsequently shown that this assumption is not very likely and that compound III is very probably formed at a later stage during the isolation procedure.

In their study of the reaction Blicke and Burckhalter report that when compound I is treated with alkali, a dissociation into phenyl vinyl ketone and methyl-

[1] A piperidine base of similar structure, 1,4-dimethyl-3-acetyl-4-hydroxypiperidine, had been isolated previously by Mannich and Ball (4) from the interaction of acetone, formaldehyde, and methylamine hydrochloride.

amine occurs, which recombine in a different ratio to give the base of compound II in the sense of the following equations

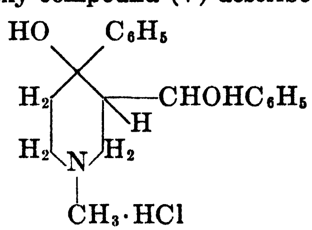
$$\text{(C)}\quad C_6H_5COCH_2CH_2NHCH_3 \rightarrow C_6H_5COCH{=}CH_2 + NH_2CH_3$$

$$\text{(D)}\quad 2C_6H_5COCH{=}CH_2 + NH_2CH_3 \rightarrow \underset{\text{Base II}}{(C_6H_5COCH_2CH_2)_2NCH_3}$$

There is no doubt that this mechanism is correct for the most part. However, these authors actually isolated the piperidine base (III) instead of the base of compound II, as they reported. It will be observed that the melting point reported by Blicke and Burckhalter agrees with that reported by Warnat for the cyclic base (III).

In testing the mechanism depicted in equations (C) and (D), Blicke and Burckhalter allowed equimolar amounts of methylamine and phenyl vinyl ketone to react. They claimed that the base of compound II was formed by this process. Again the melting point given for their base agrees substantially with that of the piperidine base (III). There is no doubt in our minds that again they were dealing with the piperidine base (III).

Because we needed substantial amounts of the piperidine base (III), which hitherto has been regarded only as a by-product in the Mannich condensation, we turned our attention to the possibility that this base might be formed as a result of treatment of compound II with alkali. This was actually found to be the case. When compound II was stirred with aqueous alkali at room temperature, an oily base was first formed. On continued stirring the oil hardened and the resulting solid could be filtered off and crystallized from methanol. The crystals melted very approximately at the temperature reported by Warnat for the piperidine base (III). The yield was excellent. The melting point of the hydrochloride was essentially that reported by Warnat. Its solubility in water was of the order of fifty percent, whereas the hydrochloride of compound II was only slightly soluble. The presence of a hydroxyl group was established by the preparation of an acetate and a propionate. Hydrogenation of the hydrochloride of III gave a dihydroxy compound (IV), distinctly different from the dihydroxy compound (V) described by Külz and Rosenmund (6).



IV

$$(C_6H_5CHOHCH_2CH_2)_2NCH_3 \cdot HCl$$

V

The easy conversion of compound II into the piperidine base (III) in the presence of alkali necessitates a re-interpretation of the results of Blicke and Burckhalter. In the light of new knowledge the reactions proceed in the following manner. The monosubstituted methylamine derivative (I) yields the piperidine base (III) by treatment with alkali. Any compound II, which might be conceived as an intermediate, would not be stable under these conditions.

The reaction of phenyl vinyl ketone and methylamine under the conditions employed by Blicke and Burckhalter yields the piperidine base (III). The alkalinity produced by the use of excess methylamine (100% excess) is sufficient to cause an isomerization of any intermediate base (II) into the piperidine base (III).

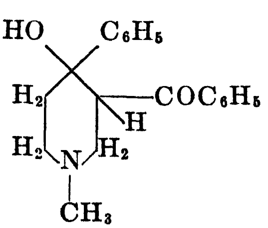
It can also be pointed out that Warnat, and also Mannich and Hieronimus, had obtained the piperidine base (III) as a secondary product because at some stage in working up their reaction mixtures they had used alkali. The use of alkali is not specifically mentioned by the above authors, but since they describe conversion of the hydrochlorides to the free bases, it is obvious they must have used alkali to liberate them.

In the course of our investigation we examined the behavior of the piperidine base (III) towards heat. When it was placed in a distillation flask, and subjected to an initial pressure of 0.2 mm., it was noticed that as distillation progressed, the pressure rose to 4 mm. When the distillation ceased, the pressure decreased to the initial value. This behavior is indicative of the loss of some very volatile material. Moreover, distillation occurred at 125–130°, a temperature considerably below that expected as the boiling point of the piperidine base (III). When hydrogen chloride was passed into an ether solution of the distillate, β-chloropropiophenone and bis-(β-benzoylethyl)methylamine hydrochloride (II) were obtained.

It can be concluded from the foregoing that distillation yielded phenyl vinyl ketone and methylamine. A considerable portion of the latter substance escaped through the oil-pump and was responsible for the increase in pressure, but some of it recombined with phenyl vinyl ketone in some part of the distillation apparatus to give the base of compound II.

There can be no doubt that we were dealing in this instance with the base of compound II and not the cyclic base. Treatment with hydrogen chloride gave the hydrochloride (II) directly. It was characterized by its analysis and by comparison of its properties with a known sample of bis-(β-benzoylethyl)methylamine hydrochloride (II). The melting points and the solubility in water were substantially the same. It was also possible to convert it into the piperidine base (III) by treatment with sodium hydroxide.

It can be argued that perhaps the piperidine base (III) might also, as a result of ring opening, form bis-(β-benzoylethyl)methylamine hydrochloride (II) on treatment with hydrogen chloride. To eliminate this possibility an authentic sample of the piperidine base (III) was treated with hydrogen chloride. A totally different hydrochloride was obtained. Thus the behavior of the piperidine base (III) on distillation can be represented by the scheme below:



III

$$\xrightarrow{\text{Distn.}} 2C_6H_5COCH{=}CH_2 + CH_3NH_2 \rightarrow (C_6H_5COCH_2CH_2)_2NCH_3$$

Base II

It is seen from the above discussion that 1-methyl-3-benzoyl-4-hydroxy-4-phenylpiperidine is not a primary product of the Mannich condensation. However, it becomes readily available when the primary products (I) and (II), particularly II, are treated with alkali.

In view of this fact, the Mannich condensation was studied further with the object of improving the yield of II. The reaction of methylamine hydrochloride, acetophenone, and paraformaldehyde could be carried out in various solvents other than alcohol. At first it was thought that some entraining agent, which removed water from the reaction continuously, would lead to improved yields. Thus benzene and alcohol, carbon tetrachloride, tetrachloroethane, and excess acetophenone were used as solvents with varying results. Mr. H. Weinhagen of our laboratory found subsequently, however, that even water can be used as a solvent for the reaction. Finally we succeeded in carrying out the condensation with no solvent at all. The reaction in this instance is extremely vigorous and is complete in 15–20 minutes with the formation of a solid cake. Because of the extreme vigor of the reaction large scale experiments are not recommended.

The investigations reported in this paper have led to an elucidation of the behavior of Mannich bases of the types $RCOCH_2CH_2NHR'$ and $(RCOCH_2CH_2)_2NR'$. The newly gained knowledge permits the preparation of certain 3,4-disubstituted piperidine derivatives in high yields.

Acknowledgment. We are indebted to Dr. A. Steyermark for microanalyses.

EXPERIMENTAL

PART I. THE CONDENSATION OF ACETOPHENONE WITH FORMALDEHYDE AND METHYLAMINE HYDROCHLORIDE

BIS-(β-BENZOYLETHYL)METHYLAMINE HYDROCHLORIDE (II)

(A) *In alcohol.* The reaction in alcohol has been adequately described by Mannich and Heilner (1), Warnat (3), and Blicke and Burckhalter (2).

(B) *In benzene–alcohol.* A mixture of 136 g. of methylamine hydrochloride, 130 g. of paraformaldehyde, 480 cc. of acetophenone, 240 cc. of ethanol, and 240 cc. of benzene was stirred and heated in a water-bath at 80–83°. A homogeneous solution resulted, the internal temperature rose to 3–7° above the bath temperature, and refluxing began. A trap in the path of the condensate separated the water in the distillate and permitted the return of the organic solvents. The bath temperature was raised finally to 90° and the material was refluxed for 6–8 hours until 80–100 cc. of the aqueous phase had separated. The mixture was cooled, and the crystals were filtered and washed with about 100 cc. of ethanol. The yield of bis-(β-benzoylethyl)methylamine hydrochloride (II), m.p. 150–155°, amounted to 63–68%. The yield can be improved by 15–20% by utilization of the mother liquor from the original reaction mixture as the solvent medium for the next batch of reagents. The crude product was satisfactory for our purposes, but it could be crystallized with an 85% recovery from 30 volumes of ethanol. The crystals thus obtained melted at 166–169°.

(C) *In tetrachloroethane.* Acetophenone (364 g.) was added to a suspension of 190 g. of paraformaldehyde, 208 g. of methylamine hydrochloride, and 700 cc. of tetrachloroethane. The mixture was heated. When the temperature reached 70°, an exothermic reaction took place. With the aid of a cold-water bath the temperature was maintained at 70–80° until all of the material had dissolved. In a vacuum of 50–70 mm., a mixture of tetrachlorethane and water was then slowly distilled off, while simultaneously an additional 362 g. of acetophenone was added to the reaction mixture. The distillate was collected in a separator

which permitted retention of the water and return of the tetrachlorethane. The mixture was maintained at 65–72° throughout the distillation, which was allowed to continue until 92 cc. of water was collected. The entire process required about one hour. Towards the end of the reaction the bis-(β-benzoylethyl)methylamine hydrochloride (II) began to precipitate. The mixture was cooled to room temperature, 900 cc. of acetone was added, and the whole was filtered in a centrifuge basket. The product, m.p. 156°, weighed 662 g. (66%). It was not pure but was satisfactory for the preparation of the piperidine base (III).

(D) *In carbon tetrachloride.* The reaction was carried out in essentially the same fashion. Only a very slight reduced pressure was applied to the system to permit a temperature of 70°. However, a reaction time of about 2.5 hours was required for complete removal of the water. The yield was 48%.

(E) *In excess acetophenone.* A mixture of 16.9 g. of methylamine hydrochloride and 242 cc. of acetophenone was stirred and heated to 80° and to it was added every four minutes 2 g. of paraformaldehyde until a total of 16 g. had been added. The thick suspension was cooled and filtered. The precipitate was digested with Skellysolve B, and then with hot alcohol. The yield of bis-(β-benzoylethyl)methylamine hydrochloride (II), m.p. 159°, amounted to 85%.

(F) *In water.* A mixture of 480 g. of acetophenone, 150 g. of methylamine hydrochloride, 306 cc. of 36% formalin, and 300 cc. of 10% hydrochloric acid was heated in a bath with stirring at 90° for 40–60 minutes until homogeneous solution resulted and then for an additional 15 minutes. The bath was removed and the mixture allowed to cool and crystallize with stirring during 15 hours. The crystals were filtered and washed with about 300 cc. of ice-cold ethanol. After drying at 40–50°, the bis-(β-benzoylethyl)methylamine hydrochloride (II) weighed 360–380 g. (54–57%) and melted at 162–163°. This preparation was first carried out by Mr. H. Weinhagen of this laboratory.

(G) *Without solvent.* A mixture of 120 g. of acetophenone, 32 g. of paraformaldehyde, and 34 g. of methylamine hydrochloride was placed in a 2-liter beaker and heated on a hot plate to about 80° with stirring. A vigorous reaction soon occurred and it was necessary to discontinue heating and stirring to avoid overflow. The solid mass of crystals thus obtained was ground in a mortar in the presence of 200 cc. of ethanol. On drying, the crystals weighed 116 g., (70%) and melted at 160–161°.

PART II. 1-METHYL-3-BENZOYL-4-HYDROXY-4-PHENYLPIPERIDINE (III)

(A) *Base.* A suspension of 1440 g. of bis-(β-benzoylethyl)methylamine hydrochloride in 16 liters of water was stirred and treated with a solution of 320 g. of sodium hydroxide in 3200 cc. of water during 30 minutes at room temperature. After about an hour the oily base, which was first obtained, solidified and the solid was filtered and crystallized from 7 liters of methanol. After standing overnight 760 g. of 1-methyl-3-benzoyl-4-hydroxy-4-phenylpiperidine, m.p. 135–136°, was obtained. The filtrate was diluted with an equal volume of water and the resulting precipitate was crystallized from 2600 cc. of acetone. An additional 272 g. of the piperidine derivative, m.p. 135–136° was thus obtained. By repetition of the dilution process 56 g. more of the piperidine derivative was obtained, m.p. 134–135°. The total yield thus amounted to 1088 g. (85%). Crystallization from methanol raised the melting point to 138–140° which is approximately that reported by Warnat (3).

(B) *Hydrochloride.* A solution of 2.0 g. of 1-methyl-3-benzoyl-4-hydroxy-4-phenlypiperidine in 175 cc. of ether was treated with gaseous hydrogen chloride. The hydrochloride weighed 1.6 g. and melted at 194–196°. The melting point depends somewhat on the rate of heating. The substance can be dissolved in water to form a 50% solution.

PART III. ACYL DERIVATIVES OF 1-METHYL-3-BENZOYL-4-HYDROXY-4-PHENYLPIPERIDINE (III)

(A) *1-Methyl-3-benzoyl-4-acetoxy-4-phenylpiperidine oxalate.* A mixture of 75 g. of 1-methyl-3-benzoyl-4-hydroxy-4-phenylpiperidine, 375 cc. of acetic anhydride, and 4 drops

of concentrated sulfuric acid was shaken occasionally during 24 hours. The crystals dissolved gradually. The solvent was removed under reduced pressure below 55°. To the cooled residue was added a solution of 60 g. of sodium carbonate monohydrate in 300 cc. of water and the mixture was stirred until effervescence had ceased. The gummy solid was taken up in 500 cc. of ether and the solution washed twice with 100-cc. portions of water. After drying with sodium sulfate the ether solution was treated with an ethereal solution of oxalic acid until no further precipitate was obtained (about 32 g. of oxalic acid). The precipitated *oxalate* was crystallized from 1100 cc. of alcohol to give 63 g. of the acetoxy derivative, m.p. 154–155°. An additional 6.8 g., m.p. 153–154° was obtained by reducing the filtrate to one-half of the original volume. The pure substance obtained by further crystallization from alcohol melted at 160–161°.

Anal. Calc'd for $C_{23}H_{25}NO_7$: C, 64.62; H, 5.90.
Found: C, 64.88; H, 5.90.

Alternatively the ether solution after drying with sodium sulfate can be distilled to dryness. Under these conditions the crude *acetoxy base*, m.p. 106–107° can be obtained. The base distilled in the presence of 2% powdered potassium carbonate at 200–203° at 0.7 mm.

(B) *1-Methyl-3-benzoyl-4-propionoxy-4-phenylpiperidine. 1. Oxalate.* A mixture of 26.2 g. of 1-methyl-3-benzoyl-4-hydroxy-4-phenylpiperidine, 12.5 cc. of propionyl chloride, and 500 cc. of toluene was allowed to stand overnight at room temperature. The precipitate (18.8 g.) was dissolved in 100 cc. of water, treated with 65 cc. of 0.972 *N* sodium hydroxide and allowed to stand in the ice-bath. The supernatant aqueous layer was decanted from the gummy precipitate which had settled to the bottom and along the sides of the container. The gummy precipitate was crystallized from 80 cc. of methanol to give 4.5 g. of unchanged starting material. The filtrate was distilled to dryness *in vacuo* and the residue was leached 4 times with 100 cc. of ether. About 1.1 g. of material remained undissolved. To the combined ether solutions, a solution of 7 g. of oxalic acid in ether was added. After standing in the refrigerator overnight, the supernatant ether was decanted from the insoluble precipitate, which was crystallized from 75 cc. of ethyl alcohol. In this manner 5.7 g. of the oxalate of 1-methyl-3-benzoyl-4-propionoxy-4-phenylpiperidine, m.p. 179–180° was obtained. Apparently the melting point depends on the rate of heating since the compound melted at 173–174° after two crystallizations.

Anal. Calc'd for $C_{22}H_{25}NO_3 \cdot C_2H_2O_4$: C, 65.29; H, 6.17; N, 3.17.
Found: C, 65.10; H, 6.35; N, 3.26.

2. Phosphate. A solution of 4 g. of the oxalate in 280 cc. of water was treated with 183 cc. of 0.1000 *N* sodium hydroxide and extracted twice with 200 cc. of ether. After adding 400 cc. of additional ether to the combined extracts, 16 cc. of 85% syrupy phosphoric acid was added with stirring. In this manner 4.45 g. of the *phosphate salt*, m.p. 178–179° was obtained.

Anal. Calc'd for $C_{22}H_{25}NO_3 \cdot 2H_3PO_4$: Neutral equivalent, 137.
Found: Neutral equivalent, 136.

PART IV. HYDROGENATION OF 1-METHYL-3-BENZOYL-4-HYDROXY-4-PHENYLPIPERIDINE HYDROCHLORIDE

1-Methyl-3-(α-hydroxybenzyl)-4-hydroxy-4-phenylpiperidine hydrochloride (IV). A mixture of 0.45 g. of platinum oxide catalyst, 115 cc. of ethanol, and 25 cc. of 1.18 *N* hydrochloric acid was shaken for a few minutes to reduce the catalyst. Then 8.7 g. of 1-methyl-3-benzoyl-4-hydroxy-4-phenylpiperidine was introduced, and hydrogenation was continued at room temperature for 24 hours. About 0.05 mole of hydrogen was absorbed. The mixture was filtered, and the insoluble precipitate was digested with 110 cc. of boiling water and filtered. From the filtrate 3.1 g. of 1-methyl-3-(α-hydroxybenzyl)-4-hydroxy-4-phenylpiperidine hydrochloride (IV), m.p. 267–268° (d), was obtained on cooling.

Anal. Calc'd for $C_{19}H_{23}NO_2 \cdot HCl$: C, 68.35; H, 7.24; N, 4.20.
Found: C, 68.07; H, 7.12; N, 4.20.

PART V. BEHAVIOR OF 1-METHYL-3-BENZOYL-4-HYDROXY-4-PHENYLPIPERIDINE TOWARDS DISTILLATION

When 25 g. of 1-methyl-3-benzoyl-4-hydroxy-4-phenylpiperidine (III) was distilled under an initial pressure of 0.2 mm., it was noticed that as distillation progressed, the pressure rose to 4 mm. When the distillation ceased, the pressure returned to approximately the initial value. At 120–130°, 16.1 g. of distillate was collected. The residue weighed 6.5 g. A small sample of the distillate titrated electrometrically with 0.1 *N* hydrochloric acid gave a neutral equivalent of 620. The remainder of the distillate was stirred with 150 cc. of ether, and the mixture filtered from a small amount of insoluble material. Hydrogen chloride was passed through the filtrate. The precipitate of bis-(β-benzoylethyl)-methylamine hydrochloride weighed 8.6 g. and melted at 157–159°. Crystallization from alcohol gave the pure compound, m.p. 169–171°. Its solubility in water was 0.100 g. in 17 cc.

Anal. Calc'd for $C_{19}H_{21}NO_2 \cdot HCl$: C, 68.76; H, 6.68; N, 4.22;

Found: C, 68.55; H, 6.79; N, 4.66.

Treatment with sodium hydroxide gave a base which was crystallized from methanol to give crystals melting at 135–136° which is the m.p. of the piperidine base (III).

β-Chloropropiophenone. The ethereal filtrate after the precipitation of the hydrochloride was evaporated to dryness *in vacuo* to give 8.6 g. of β-chloropropiophenone, m.p. 48–49°. After crystallization from cyclohexane it melted at 50–53°. To identify the compound positively, 1.0 g. of the crystallized product was dissolved in 5 cc. of ethanol and then treated with 3 drops of acetic acid and 1.2 cc. of phenylhydrazine. After completion of the reaction, the precipitate was filtered and digested in 70 cc. of hot ethanol containing 0.5 cc. of 40% sodium hydroxide. The mixture was filtered hot and the filtrate allowed to crystallize. In this manner 0.81 g. of *1,3-diphenylpyrazoline* (7) m.p. 153–155° was obtained in the form of yellow crystals. A similar procedure was utilized by Blicke and Burckhalter (2) to identify phenyl vinyl ketone.

SUMMARY

Discrepancies in the literature, concerning the products of the condensation of acetophenone, methylamine hydrochloride, and formaldehyde have been clarified. A method is described for the preparation of 1-methyl-3-benzoyl-4-hydroxy-4-phenylpiperidine.

NUTLEY, N. J.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY, UNIVERSITY OF TORONTO]

POLYMERIZATION OF β,β′-DICHLORODIETHYLAMINE

IRENE LANGMAN, A. F. McKAY, AND GEORGE F WRIGHT

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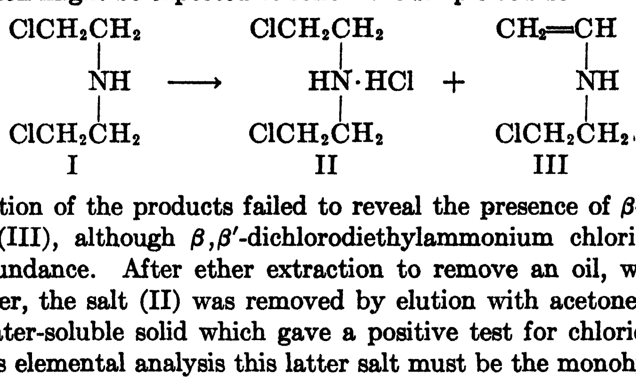
Although Ward (1) mentioned the conversion of β,β′-dichlorodiethylammonium chloride (II) to its free base (I) in terms which implied a reasonable stability for the latter compound, we have found that β,β′-dichlorodiethylamine (I) is extremely susceptible to decomposition. Only small amounts (15 g.) can be distilled without violent conversion to a charred solid. When a small distillate was obtained it began to solidify after two hours at room temperature; the reaction was complete in twelve days. This conversion could be accelerated to completion within two days with respect to the formation of β,β′-dichlorodiethylammonium chloride (II) if the amine was diluted with methanol. All the products were very soluble in water.

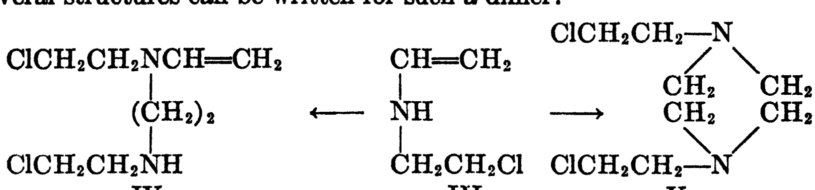
This reaction might be expected to follow the simple course:



I II III

but examination of the products failed to reveal the presence of β-chloroethylvinylamine (III), although β,β′-dichlorodiethylammonium chloride (II) was found in abundance. After ether extraction to remove an oil, which will be discussed later, the salt (II) was removed by elution with acetone. There remained a water-soluble solid which gave a positive test for chloride ion. According to its elemental analysis this latter salt must be the monohydrochloride of a dimer derived from N-β-chloroethyl-N-vinylamine (III).

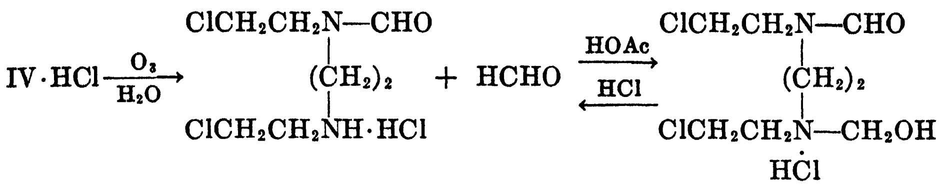
Several structures can be written for such a dimer:



IV III V

but the structure IV (as N,N′-*dis*-β-chloroethyl-N-vinyl-1,2-diaminoethane hydrochloride) is favored over that of di-β-chloroethylpiperazine (V). The latter compound ought to be strongly basic and thus form a dihydrochloride, but only the monohydrochloride was obtained. Furthermore the piperazine (V) should not give formaldehyde after ozonization although N,N′-*bis*-β-chloroethyl-N-vinyl-1,2-diaminoethane (IV) hydrochloride should yield this aldehyde. The fact that formaldehyde was obtained, even in the small yield of 5% of that theoretically possible confirms that IV is the structure of the dimer.

Certain difficulties in the ozonization procedure would seem to confirm that the dimer has structure IV. The ozonization of the salt has been carried out in formic acid. When this solvent is removed *in vacuo* and replaced by water, a qualitative test for formaldehyde (2) is obtained, but this disappears after a short time and indeed, cannot be obtained at all when the ozonide is decomposed slowly under reductive conditions (3). The reappearance of this formaldehyde was effected by boiling the aqueous solutions with hydrochloric acid. Since this is a treatment which might be expected to decompose a methylolamine, it is thought that the following sequence of reactions occurs during and after ozonization.

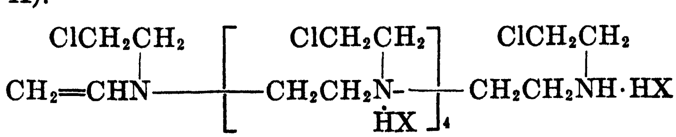


VII

Since the methylolation reaction requires either a primary or a secondary amine, the tertiary amine (V) could not have partaken in this reaction sequence.

When the salt (IV as the monohydrochloride) was dissolved in water and treated with 40% sodium hydroxide and oil separated. When this oil was dissolved in acetone and treated immediately with hydrogen chloride, about a fourth of the salt of IV was regenerated, but when treatment with hydrogen chloride was delayed it was evident that the free base represented as IV had undergone a change.

Further evidence for this change was obtained from a solution of the oil in ether (in which it was not very soluble). When this ether solution was treated immediately with picric acid a picrate melting at 215–216° was formed. This picrate gave an analysis conforming closely to $C_{54}H_{63}Cl_6N_{21}O_{35}$. This would be the formula expected if the free base represented as IV would trimerize linearly, since the terminal β-chloroethylvinylamino linkage should be too weakly basic to form a salt. In consequence only a pentapicrate (VI), and not a hexapicrate, might be expected (In the formulation the picrate radical is denoted by X).



VI

Although the analyses are in closest agreement with the pentapicrate of the hexamer of β-chloroethylvinylamine (III), it is realized that some multiple other than 4 may be the correct one for structure VI.

Compound IV (N,N'-*bis*-β-chloroethyl-N-vinyl 1,2 diaminoethane) as hydrochloride was isolated as the residue after ether and then acetone extraction of the original reaction product. Evaporation of the ether left an oil. It was not

very stable and it gradually became more viscous; the oily product was no longer soluble in ether and evidently had suffered advanced polymerization. However if the ether extract was treated immediately with picric acid an impure picrate was precipitated which, when purified, was identical with VI, the pentapicrate of the hexamer of β-chloroethylvinylamine. Identical treatment of the ether solution with styphnic acid also resulted in a precipitate which gave analysis expected for the pentastyphnate of the hexamer of β-chloroethylvinylamine.

The acetone extract from the reaction mixture was a mixture from which bis-β-chloroethylammonium chloride and the oil yielding the hexamer pentapicrate could be separated by evaporation of the acetone followed by extraction with cold ethyl acetate. The separation of these two components was effected by elution with ether in which the salt (II) was insoluble. That part of the mixture which was insoluble in ethyl acetate was a highly intractable oil of the same type obtained when the ether solution of the hexamer [corresponding to the salt (VI)] was allowed to stand.

It seems, therefore, that when bis-β-chloroethylamine is treated with alkali the original product is β-chloroethylvinylamine, but this compound is not isolable owing to its tendency towards polymerization. This polymerization stops at the dimer stage insofar as hydrogen chloride is available to stabilize the dimer as the salt of IV. However since part of the liberated hydrogen chloride will be consumed in re-formation of *bis*-β-chloroethylammonium chloride (II) the system is deficient with respect to salt formation. The free bases must then polymerize further, since a picrate or styphnate of the hexamer (VI) can be isolated. Likewise the heavy oils remaining after the identifiable products are isolated are evidently more highly polymerized.

If this mechanism is valid a decrease in the activity of hydrogen chloride should favor polymerization of the free bases. The decrease ought to be effected by the use of a hydroxylic solvent. This expectation was realized by solution of the *bis*-β-chloroethylamine in methanol. In this solvent the yields of *bis*-β-chloroethylammonium chloride (II), N,N′-bis-β-chloroethyl-N-vinyl-1,2-diaminoethane (IV hydrochloride), and the hexamer (VI) as its free base were each about 20 weight per cent of the whole, while the more highly polymerized material constituted 30 weight per cent of the whole leaving 10% unaccounted for. By contrast the decomposition without solvent yielded about 40 weight per cent each of II and IV while only a trace (0.3%) of the hexamer (VI) and only 10 weight per cent of the high polymer were obtained.

EXPERIMENTAL[1]

Bis-β-chloroethylammonium chloride. This salt was prepared essentially by Ward's method (1) in 70% yield and was crystallized from 98:2 ethanol–acetone. It melted at 214–217°.

Bis-β-chloroethylamine. Equimolecular quantities of *bis*-β-chloroethylammonium chloride (89.5 g., 0.5 mole) and aqueous sodium carbonate were mixed at 5° and the oil which separated was taken up in ether, washed with water, and dried with calcium sulfate. After vacuum distillation of the ether, the yellow oil (crude yield 86%) was distilled rapidly

[1] All melting points are corrected against known standards.

at 75–80° (6 mm.). Some decomposition accompanied every distillation at this pressure, and it was usually violent and complete if more than 15 cc. was distilled at one time. The polymeric decomposition product is soluble in water. The distillate (50 g.; 70% of theoretical; n_D^{25} 1.472) could be preserved for at least a week at −80°, but at 25° decomposition with salt precipitation commenced after several hours.

Decomposition of bis-β-chloroethylamine. The polymerization of 8 g. (0.056 mole) of *bis*-β-chloroethylamine was complete in two days in methanol solution (21 grams per cc.) but twelve days at 25° were required when no solvent was used. In the polymerization without solvent the semi-solid was boiled with 100 cc. of ether. Evaporation of the ether left a non-volatile, non-distillable oil. With age this oil was no longer soluble in ether. If, however, the ether solution was treated immediately with picric acid in ether solution a crystalline precipitate separated, and could be removed by centrifugation. It weighed 0.067 g. (0.3% yield) and melted at 214–215° or 215–216° after wasteful crystallization from toluene. A comparable decomposition in methanol gave 2 g. (9.1% yield) of *pentapicrate*.

Anal. Calc'd for $C_{54}H_{63}Cl_6N_{21}O_{53}$: C, 36.4; H, 3.57; Cl, 11.9; N, 16.5.

Found: C, 36.4; H, 3.53; Cl, 11.8; N, 16.5.

The *styphnate* was prepared and purified in the same manner.

Anal. Calc'd for $C_{54}H_{63}Cl_6N_{21}O_{40}$: C, 34.8; H, 3.39; N, 15.8.

Found: C, 34.9; H, 3.37; N, 16.0.

These analyses indicate that there must have been present in the ether-soluble oil a hexamer of β-chloroethylvinylamine $[C_4H_8ClN]_6$ which formed a pentapicrate or a pentastyphnate.

The residue remaining after ether extraction was further extracted with 100 cc. of hot acetone to leave a solid. The extract was vacuum-evaporated and the residue extracted with unheated ethyl acetate to yield an oil. Repetition of this ether–acetone–ethyl acetate extraction finally left an oil which seemed to be a polymer similar to that which precipitated from the aged ether extract. This oil is believed to be a high polymer, $[C_4H_8ClN]_n$.

The substances soluble in ethyl acetate could be separated by ether extraction into the soluble fraction which yielded (VI), the pentapicrate or styphnate of hexameric β-chloroethylvinylamine, and an ether insoluble portion which was identified as *bis*-β-chloroethylammonium chloride (II) (m.p. 215–217°).

The white amorphous solid insoluble in acetone was a salt not identical with II. It was soluble in water and this solution gave a positive test with silver nitrate for chloride ion. It melted at 322–325°. Since no proper crystallizing medium could be found it was analyzed in this form. Polymerization without solvent gave a yield of 3.1 g. (38%) while polymerization in methanol yielded 2.3 g. (30%).

Anal. Calc'd for $C_8H_{17}Cl_3N_2$: C, 38.8; H, 6.93; Cl, 43.2; N, 11.3.

Found: C, 39.2; H, 7.0; Cl, 43.2; N, 11.5.

This salt was not very soluble in methanol. When 0.2 g. of salt was dissolved in aqueous picric acid, 0.4 g. of a *picrate* was formed. This picrate decomposed without melting at a high temperature. When the water solution of this N,N′-*bis*-β-chloroethyl-N-vinyl-1,2-diaminoethane hydrochloride (IV) was treated with 40% aqueous sodium hydroxide an oil appeared. When the oil was separated immediately, dissolved in acetone and this solution treated with hydrogen chloride, about 25% of the original salt (m.p. 311–312°) was regenerated.

The oil was not very soluble in ether. When 300 mg. of the dimer (IV hydrochloride) was treated with saturated aqueous sodium carbonate, the resulting oil could be dissolved by a 6-fold extraction with 20-cc. portions of ether. The ether solution when treated with picric acid precipitated a *picrate*, m.p. 215–216°, which was identical, according to its mixed melting point, with the picrate obtained from the original ether extraction of the reaction mixture.

Ozonization studies. A solution of 1.23 g. (0.005 mole) of N,N′-*bis*-β-chloroethyl-N-vinyl 1,2-diaminoethane (IV hydrochloride) in 22 cc. of 98–100% formic acid was treated for one hour with an oxygen stream containing 13% ozone. The solvent was then evapo-

rated under 15 mm. pressure. The residue was treated with 10 cc. of water. At first this gave a positive test for formaldehyde by the Schryver method (2) but this test was negative after the solution had aged for thirty minutes.

The solution was treated with 25 cc. of concentrated hydrochloric acid and boiled under reflux for thirty minutes. Three-fourths of the solution was then distilled (until the distillate gave a negative Schryver test). This distillate was saturated with sodium chloride, filtered, and neutralized with strong sodium hydroxide and acetic acid to *p*H 3.4. A 2% solution of dimedon in dilute alkali was added (4 cc. per 100 cc. of neutralized filtrate), the mixture aged at 5° for twelve hours, and then filtered cold through a fritted-glass filter. The *formaldehyde dimedon* derivative (m.p. 189–190°) weighed 0.7 g. This represents a 5% yield of the formaldehyde expected by ozonization of IV·HCl. The yield was lower when ozonization was continued over a longer time. The residual acid solution after distillation of the formaldehyde deposited 0.32 g. of a precipitate which was filtered off and dissolved in 10 cc. of hot water. Addition of this solution to a hot solution of 0.28 g. of picric acid in 20 cc. of water gave 0.32 g. of *picrate*, m.p. 238–9° which was not analyzed. When the salt of IV was boiled with hydrochloric acid the aqueous distillate gave no Schryver test and no dimedon derivative.

A similar ozonization of ethyl acrylate also gave a 5% yield of the expected formaldehyde.

SUMMARY

1. The distillation of *bis*-β-chloroethylamine can be effected, but the distillate decomposes to form a series of salts, all of which are water soluble.

2. This decomposition evidently involves polymerization. The dimer hydrochloride has been isolated and shown by formaldehyde formation, following ozonization, to be N,N′-*bis*-β-chloroethyl-N-vinyl-ammonium chloride.

3. After hydrolysis of the ozonide the formaldehyde is consumed, probably by methylolation of the amine fragment, since the latter can be regenerated when the solution is boiled with hydrochloric acid.

4. A picrate and a styphnate of a polymer can be isolated from the polymerized mixture. According to their analyses these are the salts of hexameric β-chloroethylvinylamine.

TORONTO, CANADA

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF BUFFALO]

THE REACTION OF CYANOGEN WITH ORGANIC COMPOUNDS. I. SECONDARY ALIPHATIC AMINES[1,2,3]

HENRY M. WOODBURN, BEACHLEY A. MOREHEAD, AND W. HALLAM BONNER

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This paper is the first of a series in which will be reported the results of an extensive study of the reactions of cyanogen with organic compounds. On the basis of its inorganic reactions cyanogen has repeatedly been compared to the halogens (1, 2). Some early work even indicated that a similar comparison could be made in the field of organic chemistry. Merz (3), for example, reported that a mixture of benzene vapor and cyanogen passed through a red hot tube gave benzonitrile, terephthalic acid nitrile, and hydrogen cyanide. Desgrez (4) studied the effect of aluminum chloride and cyanogen on boiling benzene. Decomposition of the reaction products with concentrated hydrochloric acid yielded benzonitrile, benzoyl cyanide, benzil, and unidentified compounds. Vorlander (5) claimed that toluene, diphenyl, ethylbenzene, and phenetole behaved in a similar manner.

However, Machek's report (6) that catechol in aqueous solution reacted with cyanogen to give a 52% yield of 2,3-dihydroxybenzonitrile did not stand up on reexamination, and Hahn and Leopold (7) concluded later that the reaction consisted of condensation between the phenolic and cyano groups and that no nuclear substitution had taken place. Even aniline, which brominates with such extreme ease, produced symmetrical N,N-diphenyloxamidine (8) instead of aminocyanobenzene.

Brief investigation of alcohols, aldehydes, phenylhydrazine, semicarbazide, diphenylguanidine, and benzylamine (9) also showed that comparison with halogens was a poor premise on which to base predictions regarding cyanogen chemistry.

The behavior of each of the amino compounds above could be described as an aminolysis of cyanogen. Under such circumstances the absence from the literature of reactions between cyanogen and aliphatic amines was particularly intriguing. A series of preliminary experiments, consisting in the saturation of a large number of organic liquids and solutions, was, therefore, undertaken and it was quickly indicated that reactions with primary aliphatic amines, secondary aliphatic amines, aliphatic diamines, and mercaptans could be expected once the proper conditions were discovered. The investigation of these reactions has since been actively pursued and the results of one such study are reported in this paper.

[1] From the thesis submitted by Beachley A. Morehead in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June 1948.

[2] From the thesis submitted by W. Hallam Bonner in partial fulfillment of the requirements for the degree of Master of Arts, September, 1948.

[3] Part of this work was done with the support of the Office of Naval Research under Contract N7 ONR-445 Task Order No. 2.

Secondary aliphatic amines react with cyanogen at atmospheric pressure and 0° to give N-substituted cyanoformamidines according to the equation

$$R_2NH + (CN)_2 \longrightarrow R_2N{-}\overset{\overset{\large NH}{\|}}{C}{-}CN$$

The success of the reaction depends upon the purity of the reagents, the temperature and the nature of the solvent. When pure amine or an aqueous or alcoholic solution is used, tars result from which it is almost impossible to isolate a pure product. Solutions of amines in ethyl acetate, benzene, toluene, or xylene, however, react smoothly and 50–70% yields of the cyanoformamidines are obtained.

Purification of the cyanogen is also important. Unless moisture and carbon dioxide are removed, solid crystals of the carbonic acid salt of the amine separate and the yield of cyanoformamidine is reduced. The reaction of dimethylamine is especially affected by traces of moisture and must be carried out under strictly anhydrous conditions.

TABLE I
PROPERTIES OF $R_2NC({=}NH)CN$

R	B.P.°C.	n_D^{25}	M.P.°C. HNO_3 SALT	M.P. °C HCl SALT
CH_3	80/26 mm.	1.4763$^{27°}$	136–137	197–198
C_2H_5	85/15 mm.	1.4700	123	130–135
n-C_3H_7	120/34 mm.	1.4670		
n-C_4H_9	85/1 mm.	1.4650		
n-C_5H_{11}	124/4 mm.	1.4645		

The cyanoformamidines are high-boiling, colorless liquids, with faint, not unpleasant odors. Pure samples are stable, but impure samples turn dark and deposit tar on standing. Distillation of the compounds under atmospheric pressure generally results in decomposition. Miscibility with water decreases rapidly as the molecular weight increases, the di-n-propyl derivative being already only slightly soluble. Nitric and hydrochloric acid salts of the dimethyl and diethyl derivatives are easily made and being crystalline are suitable compounds for identification, analysis, or storage. Attempts to make similar derivatives of the higher molecular weight compounds have thus far resulted only in oily products difficult to obtain in a pure state.

The nature of the reaction of cyanogen with aliphatic secondary amines and the structure of the product were deduced from a careful study of the diethylamine reaction. Analysis of the product for carbon, hydrogen, and nitrogen indicated the empirical formula $C_6H_{11}N_3$. Titration of the pure substance was impossible but the nitric acid salt, easily prepared and purified, gave an equivalent weight of 190. The calculated value for $C_6H_{11}N_3 \cdot HNO_3$ is 188.

Hydrolysis with 20% sodium hydroxide produced diethylamine, sodium oxalate, and ammonia and indicated that the structure of the substance was $(C_2H_5)_2NC({=}NH)CN$.

$$(C_2H_5)_2N\overset{\overset{\displaystyle NH}{\|}}{C}CN + 2NaOH + 2H_2O \rightarrow (C_2H_5)_2NH + Na_2C_2O_4 + 2NH_3$$

To prove that the reaction had not led to diethylcyanamide, which is likewise a high-boiling liquid and conceivably could result from the reaction of a secondary amine with cyanogen,

$$(C_2H_5)_2NH + (CN)_2 \rightarrow (C_2H_5)_2NCN + HCN$$

that compound was synthesized (10) for a comparison of boiling point and refractive index. There was not the slightest doubt that the cyanamide was absent from the reaction products.

EXPERIMENTAL

Carbon and hydrogen analyses reported below were carried out on a semimicro scale, the removal of interfering nitrogen oxides being accomplished by the method of Elving and McElroy (11). Nitrogen was determined by the semimicro Kjeldahl procedure. Melting and boiling points are uncorrected.

Preparation and purification of cyanogen. Cyanogen was prepared by the familiar reaction of cupric sulfate and sodium or potassium cyanide. Tests indicated that the gas stream contained HCN, CO_2, and water. Consequently, it was passed through a purifying train consisting of two condensers to remove most of the water, a bubbler filled with silver nitrate to remove HCN, a calcium chloride tower followed by a tower containing solid sodium hydroxide to remove CO_2, and a calcium chloride or phosphorus pentoxide tower to remove the last traces of water.

N-dimethylcyanoformamidine. A solution of 25 g. (0.55 mole) of anhydrous dimethylamine in 200 ml. of anhydrous ethyl acetate was saturated with pure cyanogen gas at 0°. The gas was absorbed slowly at first but more rapidly after the reaction began. The straw-colored liquid product was fractionated at reduced pressure yielding 20 g. (38%) of colorless material, b.p. 80° at 26 mm.; n_D^{27} 1.4763.

Since the liquid was quite unstable and hygroscopic, analysis was carried out on the hydrochloric and nitric acid salts. A solution of 16 g. (0.1 mole) of dimethylcyanoformamidine was made in 300 ml. of ether to which was added, slowly and with cooling, 39 ml. (0.1 mole) of concentrated nitric acid. White crystals precipitated which on recrystallization from ethyl alcohol melted at 136–137°.

Anal. Calc'd for $C_4H_7N_3 \cdot HNO_3$: C, 30.0; H, 5.0; Equivalent weight, 160.
Found: C, 30.1; H, 5.2; Equivalent weight, 161.

The *hydrochloric acid salt*, prepared in the same manner as the nitric acid salt, was a white crystalline solid melting at 197–198°.

Anal. Calc'd for $C_4H_7N_3 \cdot HCl$: N, 31.4. Found: N, 31.4.

N-diethylcyanoformamidine. A solution of 36 g. (0.5 mole) of diethylamine in 150 ml. of anhydrous ethyl acetate was cooled in an ice-bath and saturated with purified cyanogen. Fractionation of the liquid product gave a 70% yield of a colorless liquid boiling at 85° under 15 mm. pressure, 186° under atmospheric pressure; n_D^{25} 1.4700.

Anal. Calc'd for $C_6H_{11}N_3$: C, 57.6; H, 8.8; N, 33.6.
Found: C, 58.0; H, 8.5; N, 33.5.

The *nitric acid salt* prepared as above was a white crystalline solid melting at 123°.

Equivalent weight. Calc'd for $C_6H_{11}N_3 \cdot HNO_3$: 188. Found: 190.

The *hydrochloric acid salt* melted at 130–135°.

When unpurified cyanogen was used for the saturation of an ethyl acetate solution of diethylamine (made as above), a white crystalline precipitate was present at the end of the reaction instead of a clear liquid. Filtration yielded 4 g. of solid melting at 61° which was proved to be the *carbonic acid salt* of diethylamine by analysis and comparison with a known sample.

Anal. Calc'd for $C_4H_{11}N \cdot H_2CO_3$: C, 44.4; H, 9.6; N, 10.4; Equivalent weight, 135.
Found: C, 44.7; H, 9.2; N, 11.0, Equivalent weight, 131.

Fractionation of the mother liquor under reduced pressure gave a 60% yield of N-diethylcyanoformamidine.

N-dipropylcyanoformamidine. The preparation of N-dipropylcyanoformamidine was accomplished by saturation at 0° of dipropylamine in anhydrous ethyl acetate with purified cyanogen. The colorless liquid product was obtained in a 60% yield, b.p. 120° at 34 mm.; n_D^{25} 1.4670.

Anal. Calc'd for $C_8H_{15}N_3$: C, 62.7; H, 9.8; N, 27.5.
Found: C, 62.4; H, 10.0; N, 27.6.

N-dibutylcyanoformamidine. The product from the saturation of dibutylamine in anhydrous ethyl acetate was sufficiently insoluble in water so that it could be washed before fractionation. This helped to prevent the formation of tar during distillation. Three 50-ml. portions of 10% NaCl were used to minimize the loss of ethyl acetate. After drying over magnesium sulfate, fractionation gave a 70% yield of colorless liquid boiling at 85° under 1 mm. pressure and at 240° with decomposition at atmospheric pressure; n_D^{25} 1.4650.

Anal. Calc'd for $C_{10}H_{19}N_3$: C, 66.3; H, 10.5; N, 23.2.
Found: C, 66.5; H, 10.3; N, 23.8.

N-diamylcyanoformamidine. The procedure for this preparation was that previously used for the dibutyl analog. A 60% yield of a colorless liquid boiling at 124° under 4 mm. pressure was obtained; n_D^{25} 1.4645.

Anal. Calc'd for $C_{12}H_{23}N_3$: C, 68.9; H, 11.0; N, 20.1.
Found: C, 68.8; H, 11.3; N, 20.0.

Diethylcyanamide. This compound was prepared for reference by the method of McKee (10). It was a colorless liquid boiling at 186–188°, with n_D^{25} 1.4126.

Carbonic acid salt of diethylamine. Prepared by saturating a wet solution of diethylamine in ethyl acetate with carbon dioxide. White crystals melting at 62° with decomposition into diethylamine, carbon dioxide, and water.

SUMMARY

1. Cyanogen reacts with secondary aliphatic amines dissolved in anhydrous ethyl acetate, benzene, toluene, or xylene to give reasonable yields of N-disubstituted cyanoformamidines.

2. The methyl, ethyl, *n*-propyl, *n*-butyl, and *n*-amyl derivatives have been prepared and described.

BUFFALO, N. Y.

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[Contribution from the Department of Chemistry and Chemical Engineering of the University of Pennsylvania]

A STUDY OF THE WALLACH REACTION FOR ALKYLATION OF AMINES BY ACTION OF ALDEHYDES OR KETONES AND FORMIC ACID[1]

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This manipulatively simple alkylation procedure requires heating together a primary or secondary amine, an aldehyde or ketone, and formic acid at a temperature at which carbon dioxide is evolved. The over-all reaction appears to be:

$$1.\quad >\!NH + O{=}C\!\begin{smallmatrix}\diagup R\\ \diagdown\end{smallmatrix} + HCOOH \rightarrow >\!N{-}\overset{R}{\underset{\diagdown}{C}}H + H_2O + CO_2.$$

The method is sometimes credited to Leuckart (1), who alkylated ammonia by heating carbonyl compounds with ammonium formate. Ott (2) and Ingersoll, Brown, Kim, Beauchamp, and Jennings (3) found that formamide may replace ammonium formate. Wallach (4) showed that in the presence of formic acid, alkylation of an amine by a carbonyl compound proceeds at lower temperatures, and that the method so modified is capable of considerable extension (5). The role of formic acid in the alkylation has not been wholly clear following Plöchl's observation (6) that formalin and ammonium sulfate (in the absence of added formic acid) yield methylamines and carbon dioxide, a procedure studied by Werner (7), by Brochet and Cambier (8), and by Emde and Hornemann (9, 10), and now familiar (using ammonium chloride) for the preparation of the hydrochlorides of methylamine and trimethylamine (11); it was extended to methylation of amines by Eschweiler (12).[3] Emde and Hornemann (10) reported that in this reaction one molecule of formaldehyde is oxidized for each molecule of formaldehyde reduced to N-linked methyl, and Knudsen (13) demonstrated the presence of formic acid in the reaction mixture of the Plöchl procedure. Werner (7) attributed the reduction jointly to formaldehyde and formic acid; this inference is consistent with the observation (18) that in reactions involving amine, formaldehyde and formic acid the amounts of carbon dioxide produced are less than is required by equation 1. Aldehydes other than formaldehyde, and all ketones, are ineligible to perform reduction with disengagement of carbon dioxide. The possibility that benzaldehyde might serve as reducing agent (without liberation of carbon dioxide), but so slowly that its action would be overlooked in the

[1] Paper constructed from the Ph.D. thesis of Ezra Staple, University of Pennsylvania, 1949.

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[3] To facilitate discussion the several procedures for alkylation of amines are designated as follows: (1) Plöchl-Eschweiler method: methylation of ammonia or amine by formaldehyde alone; (2) Leuckart method: alkylation involving aldehyde or ketone and ammonium formate or a formamide; (3) Wallach method: alkylation of amine by aldehyde or ketone and formic acid.

presence of formic acid, was excluded by the negative result of an experiment in which piperidine hydrochloride and benzaldehyde were heated together; no N-benzylpiperidine could be detected after a thirty-hour heating period. The similarities among the Plöchl-Eschweiler, the Leuckart, and the Wallach procedures will appear more clearly below, and justify a suspicion of identity with respect to underlying steps.

There are reported here the results of experimental studies of (*a*) the stoichiometry of the Wallach reaction, (*b*) the influences of time and temperature, (*c*) the incidence and effect of formylation, (*d*) the influence of water, (*e*) the influence of the amount of formic acid, and (*f*) the possible role of alkylidene-*bis*-amines or alkylolamines as intermediates. For the experimental study two alkylations were selected: (A) benzylation of piperidine by benzaldehyde and formic acid, and (B) formation of N-cyclohexylpiperidine from cyclohexanone, piperidine, and formic acid. These represent alkylations of secondary amine by aldehyde and by ketone and are relatively simple, involving only one stage of alkylation and permitting ready separation of the alkylated amines. To learn the fates of initial and intermediate reactants by analysis of aliquots of the reaction mixture at intervals there was elaborated for the system piperidine–benzaldehyde–formic acid an analytical procedure for the estimation of all products and reactants, excepting N-formylpiperidine. No satisfactory method was found for the estimation of the latter in the presence of other components of the mixture. Alkylations were effected in the apparatus represented by Figure 3.

(*a*) *The stoichiometry of the Wallach reaction.* The results of some experiments conducted quantitatively appear in Table I. They indicate that alkylation is representable by equation 1. In the preparation of N-benzylpiperidine yields increased with time, but throughout each experiment the molar ratios of formic acid, benzaldehyde, and piperidine consumed to carbon dioxide and benzylpiperidine formed remained close to unity. In the preparation of N-cyclohexylpiperidine this product and carbon dioxide were formed in equivalent amounts, corroborating earlier findings (19). The ratio of alkylated product and carbon dioxide was determined in many of the experimental trials referred to later, and in all cases it approximated unity. It is concluded that in these reactions the reduction is performed exclusively by the formic acid.

(*b*) *Influence of time and temperature.* The evolution of carbon dioxide usually begins near some threshold temperature, is in some cases very rapid for a time and may slacken rather abruptly, and in all Wallach reactions observed (including a number not reported here) it continued thereafter at decreasing rates for long periods (to sixty hours) and was actually never brought to a definite termination. This behavior doubtless is responsible for the extended heating periods recommended for such alkylations. The first experiment conducted quantitatively revealed for the system benzaldehyde–piperidine–formic acid an initial reaction rate unexpectedly high. In fifteen minutes (the shortest interval permitted by the manipulations involved) the reaction was 60% complete; this increased to 70% during the next fifteen minutes, after which the rate decreased markedly, with an additional yield of only 8% in four and one-half hours.

Results for the system cyclohexanone–piperidine–formic acid are qualitatively similar. The essential data are plotted as curves I and II in Figure 1, which includes also the very dissimilar time-yield curve for the reaction of N-formylpiperidine (instead of piperidine) with benzaldehyde and formic acid, discussed in section (*c*). The effect of temperature, discernible in some of the results in Tables II and IV but apparently never very pronounced, was not examined systematically. Some Wallach reactions, *e.g.*, the methylation of methylaniline (19) start at room temperature or on slight warming. Threshold temperatures

TABLE I

STOICHIOMETRY OF THE WALLACH REACTION

	REACTION PERIOD, HOURS			
	0.5	1.0	3.0	5.0
A. N-Benzylpiperidine[a]				
Reactants, moles				
Formic acid	0.98	0.97	0.95	0.93
Benzaldehyde	1.00	1.00	0.95 0.98	1.00
Piperidine	0.96	0.97	1.00 0.94	0.91
Products, moles				
Carbon dioxide	1.00[b]	1.00	1.00 1.00	1.00
N-Benzylpiperidine	0.99	0.97	0.98 0.94	0.96
Yield[c] of N-Benzylpiperidine, %	69.7	71.5	74.7 75.1	78.4
B. N-Cyclohexylpiperidine[a].				
Products, moles				
Carbon dioxide	1.00[b]	1.00	1.00	1.00
N-Cyclohexylpiperidine	0.96	0.98	0.98	0.94
Yield[c] of N-Cyclohexylpiperidine, %	17.4	27.6	29.2	31.8

[a] Piperidine, carbonyl compound, and 88% formic in ratio 1:1:2.5. Reaction temperature, 114–118°.

[b] To obtain readily comparable ratios the quantity of carbon dioxide is arbitrarily set at 1.00.

[c] Yields based on piperidine.

for the reactions under consideration were about 60° (benzylpiperidine) and 90° (cyclohexylpiperidine), but for the former there is some evidence that incipient action may occur near room temperature. There may be an optimum temperature for each reaction, as was observed by Crossley and Moore (20) for some Leuckart reactions. In practice it seems satisfactory to heat to refluxing temperatures, which in the cases reported here ranged from about 105° to 130°.

(*c*) *Formylation as a factor in the Wallach reaction.* Wallach (4) reported that formylation decreased the rate of alkylation by the Leuckart procedure and, to minimize formylation by decreasing reaction temperature, he used an excess of formic acid or formic with acetic acid, a procedure which, in view of the ease of

formylation of amines, seems not well designed to exclude formylation. Experiments to test the effects of primary formylation of the amine to be alkylated by the Wallach procedure were performed using N-formylpiperidine, benzaldehyde, and formic acid in proportions such as to duplicate conditions in the usual

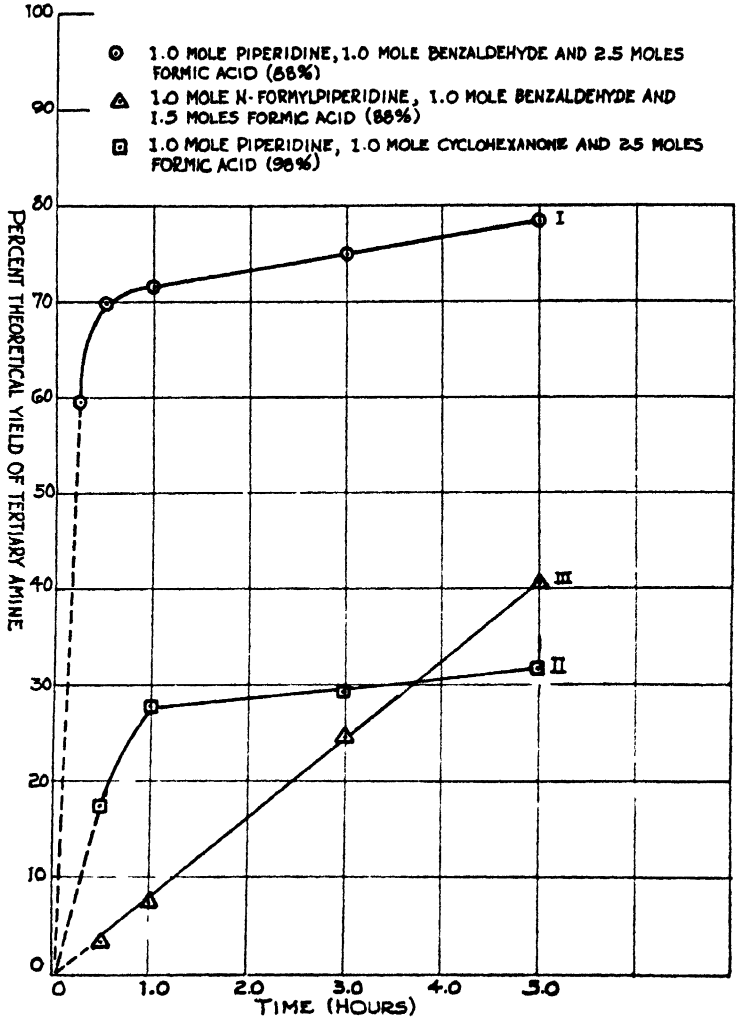


FIGURE 1. TIME-YIELD CURVES FOR WALLACH ALKYLATIONS

Wallach procedure if initial formylation of amine is complete. The results (curve III, Figure 1) are decisive in showing (a) that alkylation does occur when preformed formylpiperidine is used and (b) that the rate of alkylation is greatly depressed, the initial rapid phase being absent. Similar results were obtained in experiments with N-formylpiperidine, cyclohexanone, and formic acid.[4] It

[4] It was observed earlier (25) that both N-formylpiperidine and N-acetylpiperidine yielded N-methylpiperidine when heated with formalin and formic acid, but that reactions

seems clear that the substituted formamide is not involved in the normal sequence of reactions, and that formylation is an obstructive reaction. To decrease preliminary formylation in all subsequent experiments formic acid was added to the other reactants at ice-bath temperature, and the mixtures were warmed immediately and rapidly to reaction temperatures. The extent to which formylation occurs during the Wallach reaction must be related to the rapidity and extent of reaction during the initial phase, and it can be inferred only roughly from the time-yield curves in Figure 1. The initial rapid reaction appears to involve only amine, carbonyl compound, and formic acid. During the secondary and much slower alkylation the decrease in rate may be attributed jointly to decreasing concentrations of reactants and to presence of formylamine.

(*d*) *The effect of water.* Under usual conditions both the Leuckart and the Wallach reactions proceed in the presence of part or all of the water produced together with any initially present.[5] In the Wallach reaction it seems that the water introduced with the formic acid, or in formalin used for methylations, together with the accumulated water of reaction, has affected yields insufficiently to arouse curiosity as to its possible effects. If the first step in the alkylation sequence is the condensation of amine with carbonyl compound it appears certain that water in presence of acid will interfere, especially in reactions with ketones.

In experiments to test the influence of water the molar porportion of formic acid was kept constant but the concentrations of the acid were varied from 99% to 70%, with water as diluent. The results, in Table II, show clearly the unfavorable influence of water in substantial amounts, and that the effect is greater with ketone than aldehyde. To test the possible advantage of practically anhydrous conditions experiments were performed with anhydrous calcium sulfate[6] present in amount sufficient to combine with the water present in the 99% formic acid and that formed in the reaction. The results in Table II show that, associated with approximately anhydrous conditions, there is a small but consistently positive effect, which is somewhat greater in the presence of cobalt salt ("indicating Drierite").[7] Chemical removal of water was attempted by operation in presence of N-formylpiperidine (26), but the resulting small increase (5%) in the yield of N-cyclohexylpiperidine cannot be attributed solely to dehydration by formylpiperidine since this process liberates piperidine and formic acid which

were slow (yielding respectively 54% in 47 hours and 45% in 44 hours) as compared with those with piperidine, formalin, and formic acid (74% in 36 hours). Horning and Schock (30) made preparative use of this alternative for methylation of amine obtained as formyl derivative. In the present study N-acetylpiperidine, benzaldehyde, and formic acid yielded only 7.9% of N-benzylpiperidine in 3 hours.

[5] In the Leuckart procedure water is sometimes removed progressively by distillation, but probably never so promptly or completely as to keep the reaction mixture anhydrous.

[6] Calcium sulfate is considered preferable to other common drying agents because it does not decompose formic acid and retains one-half molecule of water below 163°.

[7] This favorable influence, like that of anhydrous magnesium chloride in the experiments of Webers and Bruce (24) using benzophenone, may be exerted upon the initial condensation of carbonyl compound and amine; Reddelien (34) reported a similar effect due to anhydrous zinc chloride in condensations of amines with ketones.

are reactants. In the aggregate these results indicate that water exerts a retarding effect upon the Wallach reaction. A more decisive test under the anhydrous conditions secured by using instead of piperidine and benzaldehyde the preformed product of their condensation, benzylidene-*bis*-piperidine, is discussed in section (*f*).

(*e*) *The effect of amount of formic acid.* The operation of formic acid as a reducing agent in the Wallach (and perhaps also the Leuckart) reaction involves its aldehydic function. If the acid properties of formic acid have a negligible or a favorable effect a large excess of acid should intensify reduction and promote alkylation. If its acid character leads to reactions which obstruct essential earlier steps in the alkylation sequence it is to be expected that for each reaction there can be found an optimum quantity of formic acid and clear indications that

TABLE II

INFLUENCE OF WATER ON THE WALLACH REACTION[a]

CARBONYL COMPOUND	FORMIC ACID CONC., %	RACTION TEMPERATURE, °C.	N-ALKYLPIPERIDINE 3-HR. YIELD, %
Benzaldehyde	99	123–125	85.6
	98	122–124	84.5
	98	104–106[b]	75.0
	88	115–117	76.0
	88	104–105[b]	61.7
	70	105–106	53.4
In presence of $CaSO_4$ (Drierite)	99	123–125	88.2
$CaSO_4$ (Indicating Drierite)	99	123–125	93.5
Cyclohexanone	99	114–116	29.2
	88	111	15.2
	70	107	7.7

[a] Piperidine, carbonyl compound and formic acid in ratio 1:1:2.5. Water introduced in diluted acid.

[b] Reaction at temperature of mixture containing 70% formic acid, to eliminate temperature effect.

excessive acid is detrimental. In experiments to test these points alkylations of piperidine by benzaldehyde and by cyclohexanone were effected with quantities of formic acid (98%) which ranged from 1 to 5 equivalents. The results, in Table III, reveal that the large amounts of formic acid hitherto specified, *viz.*, 4 to 5 equivalents by Wallach (4) or 2.5 equivalents by Clarke, Gillespie, and Weisshausz (18), are harmful and wasteful; the highest yields are obtained with only one equivalent of formic acid.[8] This means that formic acid is an effective reducing agent even in the low concentrations present late in the reaction, and permits the inference that if formic acid functions as an acid it may be as an acid catalyst; this view is considered in section (*g*).

[8] Yields with one equivalent of formic acid are probably affected by a negative error owing to the fact that stratification of the reaction mixture occurred (in absence of excess formic acid which keeps the mixture homogeneous), thus decreasing the yield obtainable in 3 hours.

In alkylation with only one equivalent of formic acid the reaction mixture becomes basic, for the total of the basic compounds remains constant while the acid is progressively destroyed. To test whether or not alkylation will occur in continuously basic environment an experiment was performed using two equivalents of piperidine and one each of benzaldehyde and formic acid. The yield of 72% in three hours showed that these conditions are not optimal but that a predominantly acidic environment is not essential. The unfavorable influence of a large excess of formic acid may be attributed jointly to repression of the dissociation of amine formate, to obstruction of condensation of amine and carbonyl compound, and to formylation of amine.

(*f*) *Interaction of benzylidene-bis-piperidine and formic acid.* The effects of water, and of excess formic acid, are believed to be adverse because these agents interfere with primary condensation of amine and carbonyl compound, which condensation liberates water and must be progressively impeded by its accumulation. Exclusion of the condensation step by use of the preformed condensation

TABLE III

INFLUENCE OF AMOUNT OF FORMIC ACID

CARBONYL COMPOUND	FORMIC ACID 98%, EQUIV.	REACTION TEMPERATURE, °C.	N-ALKYLPIPERIDINE 3-HR. YIELD, %
Benzaldehyde	1.0	114–116	83.2
	2.5	122–126	81.6
	5.0	122–125	69.4
Cyclohexanone	1.0	110–112	61.7
	2.5	114–116	29.2
	5.0	120–122	12.8

product should therefore improve the conditions for alkylation. Clarke, *et al.* (18), found that methylene-*bis*-amines and formic acid produced methylated amines in good yields, though these results led to no important conclusions. This matter has now been examined, for the preparation of N-benzylpiperidine, by heating preformed benzylidene-*bis*-piperidine[9] with formic acid. The results of these experiments were impressively different from those under other conditions. Reaction started spontaneously at or below room temperature, and without application of heat was 75–80% complete when gas evolution subsided. Upon heating the mixture as usual for the remainder of a three-hour period the yield of benzylpiperidine was 100%. It thus appears that by use of the preformed condensation product the optimum conditions for this alkylation are attained.

[9] Benzylidene-*bis*-piperidine appears to be the only known condensation product of benzaldehyde and piperidine. Laun (27) was unable to obtain the aminocarbinol, and in the present study attempts to make and isolate it were unsuccessful. If present in the Wallach reaction it would probably be converted thermally (28) to benzylidene-*bis*-piperidine. No similar condensation products of piperidine and cyclohexanone are known; Mannich and Davidsen (29) obtained only the secondary product N-(1-cyclohexenyl)piperidine.

In these experiments the formic acid was present in appreciable excess; since benzylidene-*bis*-piperidine represents two equivalents of amine the usual amount of formic acid was doubled. It is noteworthy that so considerable an excess of acid above that required for reduction (sufficient markedly to decrease yields when the starting compounds are piperidine and benzaldehyde) has no adverse effect upon conversion of benzylidine-*bis*-piperidine to benzylpiperidine. The inference is clear that excess formic acid impedes the primary condensation but not the subsequent reduction of the condensation product. If this condensation product is an essential intermediate, initial conditions in the usual Wallach reaction should be such as to encourage its formation, *viz.*, 2 equivalents of amine to one of carbonyl compound and no undue excess of acid. To ascertain the effects of such conditions experiments were performed in which carbonyl compound, piperidine, and formic acid were present in the ratio 1:2:2.5. Inter-

TABLE IV

COMPARISON OF WALLACH ALKYLATIONS UNDER VARIOUS CONDITIONS

REACTANTS	MOLAR RATIO	N-BENZYLPIPERIDINE		N-CYCLOHEXYLPIPERIDINE	
		3-hr. yield, %	Reaction Temp., °C.	3-hr. yield, %	Reaction Temp., °C.
Benzaldehyde, Piperidine, 98% Formic Acid	1:1:2.5[a]	81.6	114–117	29.2	114–116
	1:2:1[b]	72.1	104–114		
	1:1:1	83.2	114–116	61.7	110–112
	1:2:2.5[c]	97.9	112	80.8	114–116
Benzylidene-*bis*-piperidine, 98% Formic Acid	1:2.5[d]	100	135		

[a] These are the customary proportions (18).
[b] Experiment in basic environment.
[c] Proportions favorable for formation of alkylidene-*bis*-piperidine.
[d] Based on piperidine represented; 5 equivalents based on benzylidene-*bis*-piperidine.

action of benzaldehyde, piperidine, and formic acid started feebly at room temperature and on heating as usual was initially vigorous; the yield of benzylpiperidine after three hours was 97.9%. A similar experiment with cyclohexanone, piperidine, and formic acid produced a yield of 80.8%, that by the usual procedure being 29%. In these experiments piperidine was present as formate, and the excess formic acid served at first to keep the mixture homogeneous, but was consumed as reaction progressed, so that after the alkylation reached 50% the bases were present in excess.

The experiments with preformed condensation product, and those using conditions favorable to its formation *in situ* thus produced the highest yields of alkylated amine yet reported; the next best yields resulted when carbonyl compound, amine, and formic acid were used in equivalent amounts. Table IV permits comparison of the results using several reaction conditions.

(*g*) *The course of the Wallach reaction.* Results presented above are believed to be significant with respect to the course of the Wallach alkylation and, in

conjunction with some earlier results with analogous systems, permit extension of the view that a common basis exists for a number of reactions of amines and carbonyl compounds in presence of acid and for certain hydrogenation-dehydrogenation reactions involving amines and aldehydes or ammono-aldehydes. It was shown in section (*c*) that formylamine (formamide) is not a normal intermediate in the Wallach reaction, but that formylation may not be avoidable, so that part (or much) of the alkylated product may be derived from the formylamine; to this extent the reaction may be considered to be a Leuckart reaction with added formic acid (3, 20). For this reason the Wallach reaction cannot be discussed apart from the Leuckart reaction.

The course originally suggested for the Leuckart reaction (using ammonium or amine formate) by Wallach (4) involves primary thermal dissociation of ammonium formate into ammonia and formic acid, followed by additive union of ammonia and carbonyl compound to yield an α-aminocarbinol, and reduction of this by formic acid, analogous to the reduction of triphenylcarbinol to triphenylmethane by formic acid (31). Emde (9) represented the reduction step to occur by thermal decarboxylation of the ester produced by interaction of the α-aminocarbinol and formic acid. Alexander and Wildman (21) considered such esters to be improbable intermediates, apparently judging them to be of the "homo-polar" type (*e.g.*, methyl or benzyl formate) found by Bowden, Clark, and Harris (32) to require temperatures from 200° to 400° for decomposition, rather than of the "polar" type [*e.g.*, triarylmethyl and related formates (33a)] which decompose at much lower temperatures.

The demonstration that formamides can be used in the Leuckart reaction (2, 3) led to speculation as to the manner of their involvement. The relatively high temperatures (150–200°) used would suffice to convert ammonium or amine formates to formamides, but a conclusion that the alkylation proceeds via the formamide cannot well be reconciled with Alexander and Wildman's finding (21) that ammonium formate reacts under conditions so mild that formamide fails to react, which result appears to confirm the claim of Crossley and Moore (20) that formamide is not an essential reactant. The contrary view has not been abandoned (22, 23, 24); it assumes initial addition of formamide to carbonyl compound to form an intermediate aminohydrin RC(OH)NCHO reducible to RCHNCHO (formyl derivative of alkylated amine). This view finds partial support in the observation of Nabenhauer (17) that N,N-dialkylformamides, which are incapable of such condensation, do not yield tertiary amines by the Leuckart procedure. They do so, however, in the presence of formic acid, and this result is consistent with the favorable effect of formic acid added to the usual Leuckart reactants (3, 20). Webers and Bruce (24), in seeking an explanation for the apparent catalytic effect of ammonium salt (and of anhydrous magnesium chloride[7]) upon the Leuckart reaction, assumed formation of the same intermediate by the addition of a proton (from ammonium salt) to the carbonyl compound and addition of the resulting carbenium-oxonium ion to formamide;

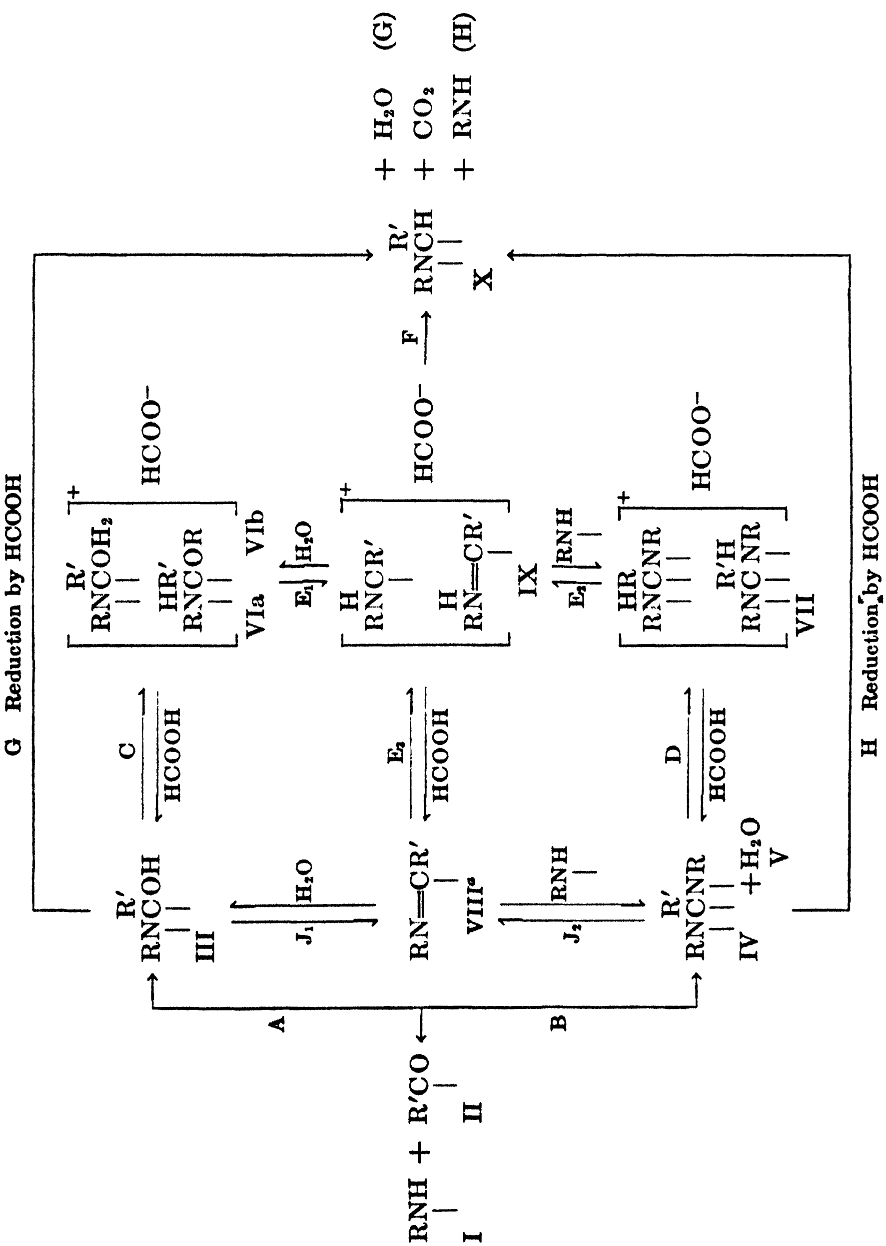
it should not be overlooked that ammonium salt may serve also as a source of ammonia which may be a reactant.

These views as to the course of the Leuckart reaction have led to no generally accepted conclusion. Speculations which involve formamide as an essential reactant cannot apply to the Wallach reactions reported here, since formylpiperidine is incapable of additive union with carbonyl compounds. Development of the view that the Leuckart and the Wallach reactions involve a single essential mechanism leads to a reaction course in which the earlier ideas of Wallach and of Emde are recognizable. The primary reactants are assumed to be ammonia (amine), carbonyl compound, and formic acid. In Leuckart reactions in which formamide is used the availability of ammonia and of formic acid may be attributed to thermal dissociation of formamide into ammonia and carbon monoxide,[10] and to condensation of ammonia with the carbonyl compound with liberation of water, which hydrolyzes formamide to yield the essential reactants, ammonia and formic acid. The condensation product is hydrogenated by the latter compound. In this way the needed reactants may be available throughout the reaction. The presence of much water, at the high temperatures used, would interfere as was shown experimentally by Crossley and Moore (20), probably by impeding condensation of amine and carbonyl compound. Complete absence of water, or its continued removal by a dehydrating agent, would decrease the yield of alkylated amine, as was observed by Alexander and Wildman (21), because in this case the only source of ammonia is the thermal dissociation of formamide, which results in loss of potential formic acid (as carbon monoxide) needed for reduction.[11] In practice the initiation of Leuckart reactions of formamides may include also the hydrolytic effect of water incidentally present. As thus represented the Leuckart and the Wallach reactions are identical throughout the actual alkylation sequence. The Wallach reaction uses as starting materials the essential reactants, which in the Leuckart procedure are obtainable, in preliminary steps, from ammonium or amine formate or from a formamide.

A suggested course of the Wallach reaction, presented in the accompanying diagram (Figure 2), is based jointly upon evidence reported above and upon analogies with systems studied earlier. The principal steps are the condensation of amine and carbonyl compound to yield intermediates such as hydroxyalkylamines, alkylidene-*bis*-amines or (from primary amines) alkylidene-imines or Schiff bases; reduction of the condensation product to alkylamine by formic acid by two alternative paths, one represented as a sequence initiated by formation of a salt of the condensation product and terminated by transfer of

[10] Formamide dissociates readily on heating (23, 24). Some thermal dissociation of N-formylpiperidine may be inferred from the results of experiments with this as a starting compound [section (*c*)], for the amounts of formic acid consumed exceeded by 20–30% the amounts of carbon dioxide formed, contrasting with the deviations of 2–7% from the 1:1 ratio observed in experiments with piperidine, benzaldehyde, and formic acid (Table I).

[11] It is possible that formamide, functioning as aquo-ammono-formic acid, *i.e.*, as an aldehyde, may effect hydrogenation [*cf.* (40)]. This also would lead to decreased yields of alkylated amine.



[a] Schiff base from primary amine.

FIGURE 2. Course of Wallach Alkylation.

hydrogen from the aldehydic grouping of the formate ion, and the other a unidirectional hydrogenation-dehydrogenation of Cannizzaro type involving formic acid (as carbonic aldehyde) and an ammono-aldehyde or ammono-ketone.

Interaction of primary and/or secondary amines with carbonyl compounds is believed to be initially additive, yielding hydroxyalkylamines (III; reaction A), readily and often spontaneously convertible to alkylidene-*bis*-amines (IV; reaction B) (28, 35, 36) or to Schiff bases (VIII; reaction J). Alkylidene-*bis*-amines (IV) from aldehyde and primary or secondary amines are familiar (28, 37); generally either IV or VIII can be obtained from primary amines (reaction J) by suitable adjustment of conditions (37, 38). Compounds of types III, IV, and VIII, though susceptible to acid hydrolysis, may form in the presence of water and acid[12] (36), and seem qualified to serve as transient intermediates in the Wallach alkylation if it involves their irreversible removal as represented. No such compound from cyclohexanone and piperidine is known, hence this intermediate can only be assumed, but benzylidine-*bis*-piperidine, the only known condensation product of benzaldehyde and piperidine, was indicated to be a plausible intermediate by its quantitative conversion to benzylpiperidine by formic acid.

No direct evidence is available, or is expected, to establish the presence of the carbenium-ammonium salt IX obtained from VI, VII, or VIII respectively by loss of water (reaction E_1), or of amine (reaction E_2), or by addition of acid (reaction E_3). Analogous hypotheses have been invoked to explain certain acid-catalyzed dehydrations and deaminations; assumption of the intermediate operation of carbenium ion IX has proved helpful in elucidation of several acid-induced reactions (39, 40), and of problems of mechanism presented by other reactions studied in this laboratory (41).

The results in Table I indicate that a quantitative transfer of hydrogen from formic acid to the group $C_5H_{10}N\cdot\underset{H}{\overset{|}{C}}\cdot C_6H_5$ occurs; in Figure 2 this is represented (reaction F) to involve the two ions of the salt IX. The hydrogen must be transferred as hydride ion, as in certain organic redox reactions (33b, 42), and the reduction resembles in a formal sense a unidirectional crossed Cannizzaro reaction (40). It is interesting to observe that compound IX is actually, in highly polar form, the ester intermediate proposed by Emde (9), who assumed it to be formed by action of formic acid on the hydroxyalkylamine (III). In Figure 2 the formation of IX is represented to involve condensation products III, IV, or VIII and in such manner as to endow compound IX inevitably with the high polarity found by Bowden, Clark, and Harris (32) to be requisite to decarboxylation and transfer of hydrogen at temperatures within or near the range effective for Wallach reactions. It cannot be stated whether the primary change is decarboxylation or transfer of hydrogen; the latter was admitted by McLaughlin and Wagner (40) to account for a similar reaction which involved no decarboxylation and which the presence of acid occurred at a much lower temperature.

[12] Benzylidene-*bis*-piperidine was observed to dissolve in cold concentrated formic acid without detectable decomposition to benzaldehyde and piperidine.

Paths G and H are suggested because of the possibility that reductions of III, IV, or VIII [the last two shown to be functionally aldehydic (44)] may be reactions of unidirectional Cannizzaro type, with formic acid functioning as an aldehyde which invariably serves as a hydrogen-donor When the carbonyl compound represented is a ketone, the direction of the hydrogen-transfer is further fixed by the fact that compounds III, IV, or VIII can then serve only as hydrogen-acceptors. The Plöchl-Eschweiler reaction has been assumed to include two operations of Cannizzaro type (7, 43). Direct reductions of Schiff bases (VIII) by formic acid were reported to fail, yielding at most tarry products without gas evolution (18, 21), but by use of triethylammonium formate instead of formic acid Alexander and Wildman (21) obtained a high yield of benzylaniline from benzylidine aniline. These results are now explicable, for it seems clear that formic acid functioned as an acid but that in triethylammonium formate, which lacks acid character, the combined formic acid was able to function as an aldehyde.

Practical considerations. The findings reported above may be applied to the selection of favorable conditions for the Wallach reaction, which is a preparative procedure of some utility. The suggestions ventured here apply to mono-alkylation and will require alteration when dialkylation is intended; further they are based on results of the two cases studied and may require modification as applied to other groups of reactants.[13]

For general purposes a mixture of equivalent amounts of amine and carbonyl compound may be treated, at low temperature, with one equivalent or slightly more of formic acid of high concentration (at least 88%; probably best 99–100%), and the mixture brought promptly to reaction temperature, which is maintained for about three hours if reaction is initially vigorous or longer if it is not. The use of larger amounts of formic acid, or of acid of lower concentration, may decrease the yield of alkylated product; in any case the water present should be minimal. If the amine and carbonyl compound yield an isolable compound of type III, IV, or VIII it may be advantageous to treat this preformed compound with formic acid or with the formate of a tertiary base such as triethylamine. Increased yields may result also by use of amine, carbonyl compound, and formic acid in the ratio 2:1:2.5. In this procedure, and in the preceding one if alkylidene-*bis*-amine is used, at least one-half of the original amine is finally present. If this interferes with isolation of the alkylated product (as in the preparation of N-methylpiperidine, which is not easily separable from piperidine) the procedure may be without advantage. For rapid reaction the extent of formylation should be minimal; this is not wholly controllable, but is favored by suggestions given above. It is possible, however, to alkylate formylamines and also acetylamines by extended heating with carbonyl compound and formic acid. Alkylation by the Wallach procedure tends to be exhaustive and is most useful for preparation of tertiary amines. The Leuckart procedure permits preparation of primary amines (from ammonium formate or formamide) or of secondary amines (from N-substituted formamides) (14, 15, 16), but preparation of tertiary amines from

[13] Reports as to the utility of these suggestions are invited.

N,N-disubstituted formamides requires the presence of formic acid (17). The two procedures are therefore usefully complementary. The findings reported above for the Wallach reaction, considered in their applicability to the Leuckart reaction, make it appear that the conditions of the latter are actually unfavorable for rapid and extensive alkylation.

EXPERIMENTAL

Primary reactants (Eastman, Paragon, Baker and Adamson) were purified as follows. *Piperidine* was dried over sodium hydroxide and distilled; the 105–106°[14] fraction was used. *Benzaldehyde*, preserved with hydroquinone, was distilled under nitrogen and the 176–177° fraction was collected under nitrogen and stored in well-stoppered bottles; freshly distilled material was used for each series of experiments. *Cyclohexanone* was dried over magnesium sulfate and distilled; the 155° fraction was used. *Formic acid* of nominal 90% and 98–100% concentrations was used generally without purification, but was assayed by the mercurous chloride method outlined later and was found to contain respectively 88% and

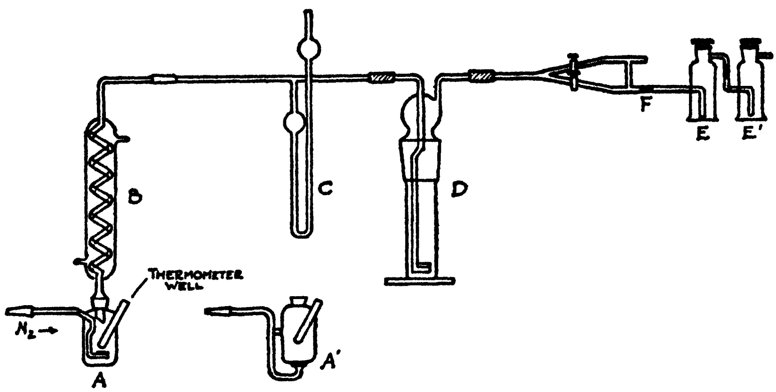


FIGURE 3

97.5–98.5% formic acid by weight. To obtain a more concentrated acid the 98% material was treated for several days with anhydrous copper sulfate[15] and was distilled in an all-glass apparatus with exclusion of atmospheric moisture. The 100.5–101° fraction was submitted to concentration by partial freezing (four repetitions) with separation of the solid phase at about 5°. The resulting acid assayed 99.5%. *N-Formylpiperidine*, b.p. 218–220°, was made by the method of Auwers (47), and *N-acetylpiperidine*, b.p. 226°, by the method of Hofmann (48). *Benzylidene-bis-piperidine* was made from benzaldehyde (21.2 g.; 0.2 mole) and piperidine (34.0 g.; 0.4 mole), which reacted spontaneously, the mixture solidifying; to complete the reaction the mass was warmed below 50° for 15 minutes and was then crystallized twice from 95% ethanol. The pure product (33.6 g.; 65%) melted at 80–81° (corr.), the value given by Laun (27). *Piperidine hydrochloride* was prepared by passing hydrogen chloride into a solution of piperidine in absolute ethanol. The washed and air-dried salt melted at 244° (corr.); Vorländer and Wallis (49) reported 245°.

Apparatus (Figure 3). The reaction vessel A, capacity about 50 ml., is provided with a gas inlet tube with sintered-glass diffusion disc and a thermometer well. Reaction vessel A′ is used when reaction mixtures include solid dehydrating agents in order to assure

[14] Melting points and boiling points are "observed" values unless otherwise specified.

[15] Copper sulfate is probably incapable of yielding anhydrous formic acid, but more rigorous treatment, such as elaborate fractionation or use of boric anhydride (45) was judged inadvisable in view of the reported instability of very concentrated formic acid (46).

effective agitation by the gas stream. The flask is joined to a wide-bore reflux condenser B, and this to a tube with a branch to a mercury manometer C (to this point all connections are glass) and connected to a gas-washing bottle D the inlet tube of which ends in a sintered-glass gas diffuser. Absorber D contains concentrated sulfuric acid and serves as a trap to remove traces of formic acid from the gas stream. The manometer indicates internal pressure before the acid trap and serves as a safety valve in case excessive pressure develops during rapid reactions. Two absorption bottles E and E′ (Stetser-Norton type), containing Ascarite, are connected in series to F, which provides a relief outlet as shown. During the entire course of each experiment, except the period of active evolution of carbon dioxide, there is passed a stream of nitrogen; this is used instead of air to exclude the possibility that carbon monoxide (from the reaction or from formic acid decomposed in the acid trap D) might be oxidized to carbon dioxide and absorbed by the Ascarite. The effectiveness of these precautions was tested by refluxing 90% formic acid in the apparatus, with the highest manageable flow rate of nitrogen; after 3 hours the gain in weight of receivers E and E′ was less than 1 mg.

PROCEDURE FOR ANALYSIS OF REACTION MIXTURES FOR FORMIC ACID, BENZALDEHYDE, PIPERIDINE, AND N-BENZYLPIPERIDINE

Formic acid is estimated in a separate portion, following a preliminary acid hydrolysis to obtain any formic acid bound as N-formylpiperidine (for determination of which in these mixtures no satisfactory method could be devised), by an adaptation of the method of Franzen and Egger (50). A sample containing about 0.1 g. of formic acid is heated under reflux for an hour with 25 ml. of 10% hydrochloric acid. The solution is made slightly alkaline with sodium hydroxide and is then evaporated to dryness on a steam-bath, to remove amines and benzaldehyde. The solution of the residue in water is made slightly acid with hydrochloric acid and is treated with 30 ml. of mercuric chloride reagent ($HgCl_2$ 100 g., NaCl 150 g. per liter). Water is added to a volume of about 300 ml., and then 10% sodium hydroxide solution to faint permanent turbidity, followed by 30 ml. of saturated sodium acetate solution. The volume is increased to 400 ml., and the mixture is kept in a steam-bath for 6 hours, and is then cooled to room temperature. The mercurous chloride is collected in a weighed glass filter crucible, washed sparingly with water and then with 95% ethanol, dried to constant weight at 105° and weighed.

Benzaldehyde is estimated in a separate portion of the reaction mixture, using the method of Houghton (51). The aliquot taken, containing about 0.25 g. of benzaldehyde, is treated with 5 ml. of 95% ethanol followed by 50 ml. of water, and to the clear solution is added, with stirring, a solution of 0.30 g. of 2,4-dinitrophenylhydrazine in 50 ml. of 2 *N* sulfuric acid. After 30 minutes on a steam-bath the mixture is cooled and the precipitate is collected in a weighed glass filter crucible, washed with 2 *N* sulfuric acid to remove precipitant, then with water to remove acid, and is dried at 110° and weighed. This method is satisfactory only if the benzaldehyde is nearly equivalent to the reagent used, as the low solubility of dinitrophenylhydrazine causes it to separate if present in considerable excess.

Piperidine and *N-Benzylpiperidine* are estimated in a portion of the reaction mixture containing about 0.5 g. of the amines, using a procedure based upon the solubility of piperidine and the virtual insolubility of benzylpiperidine in water and upon the fact that piperidine is so effectively salted out from aqueous solution by sodium hydroxide as to be rapidly and completely extractable in ether. In order to estimate piperidine present as formylpiperidine as well as free piperidine the aliquot is first refluxed with hydrochloric acid as outlined above. Benzaldehyde is then removed by steam-distillation. In the residual liquid, chilled in ice, is dissolved sodium hydroxide sufficient to produce a concentration of 20%. The mixed amines are extracted into ether; three extractions usually suffice. The ether solution is extracted with numerous small portions of 10% aqueous sodium chloride solution until the piperidine is all present in the aqueous extract, in which it is titrated with 0.1 *N* acid, using Methyl Orange as an indicator; it is easy in this way to make certain of the extraction of all the piperidine. The ether solution containing the benzylpiperidine,

in a side-arm flask, is heated just sufficiently to evaporate the ether; more vigorous heating may cause loss of benzylpiperidine from the wet liquid. The residue in the flask is dissolved in 95% ethanol and the benzylpiperidine is titrated with 0.1 *N* acid to an end-point with Methyl Orange.

The procedures described were first tested individually and were then applied to a simulated reaction mixture, with the following results.

	TAKEN	FOUND
Formic acid	38.8%	38.2 ± 0.3%
Benzaldehyde	27.4%	26.5 ± 0.2%
Piperidine	20.3%	19.5 ± 0.0%
N-Benzylpiperidine	10.2%	11.4 ± 0.1%

The errors, negative for the first three compounds (but not exceeding −5%), and positive for benzylpiperidine, are believed to represent small actual changes in the composition of the mixture due to incipient reaction prior to analysis, as suggested also by the evolution of some bubbles of gas. The error of about +10% for benzylpiperidine is without serious effect for it was found that the amount of this product is accurately indicated by the amount of carbon dioxide produced.

N-Cyclohexylpiperidine is isolated and estimated by the following procedure devised by Borkowski (19). A weighed aliquot of the reaction mixture is refluxed with hydrochloric as outlined above to hydrolyze formylpiperidine, and the solution is made just alkaline and is extracted with ether to remove cyclohexylpiperidine (and some piperidine). The ether extract is dried over potassium carbonate and transferred to a small separatory funnel (with necessary rinsings with ether), from which it is admitted dropwise into a dried and weighed semimicro distillation outfit (consisting of a 25-ml. distillation flask with a small condenser sealed to the side-arm) which is warmed on a steam-bath, permitting removal of ether and accumulation of the amines in the flask. When the ether has been transferred, the separatory funnel is replaced by a thermometer, and the flask is heated with a small flame until piperidine (b.p. 106°) has distilled and the vapors reach a temperature of about 215–220°. A weighed receiver is now attached, and a few drops of distillate are collected to verify the boiling point of the residue; cyclohexylpiperidine boils at 230°. The entire apparatus, including the receiver is cooled and weighed, and the increase is recorded as N-cyclohexylpiperidine. Tests showed this procedure to be capable of results accurate to within 2%.

GENERAL PROCEDURE FOR THE STUDY OF WALLACH ALKYLATIONS

The reactants, previously chilled in an ice-bath, are mixed as specified below for individual experiments, and a portion (usually about 20 g.) of the mixture is weighed into reaction vessel A (the total weight also is recorded); the remainder is reserved for analysis. The apparatus is assembled, with temporary omission of absorbers E and E′, and is flooded with nitrogen for 15–20 minutes. The weighed absorbers are attached, the time is noted, and the reaction mixture is warmed by raising a preheated oil-bath (Fisher Bath Wax) so as to immerse the flask A. The bath is heated by a "micro" burner with sensitive gas control, the process being adjusted so that the time required to induce vigorous reaction or refluxing is 5–6 minutes and is reproducible. The reactions under consideration are both exothermic, and initially and briefly they may reach temperatures a few degrees above the temperature of steady refluxing. *Zero time* for the reaction is taken as the moment the mixture reaches the highest observed temperature, which is usually coincident with onset of refluxing. During the period of active evolution of carbon dioxide little or no nitrogen is passed, but as the reaction subsides and steadies the stream of nitrogen is increased to a moderately rapid rate and is continued for the duration of the reaction period. A drift of several degrees in reaction temperature may occur as the composition of the mixture changes with the progress of the reaction. At the end of the heating period the oil-bath is withdrawn, the reaction flask is wiped, and it is immersed in an ice-bath. The time when the cooling bath is substituted for the heating bath is taken as the end of the reaction period. Since the cooling

period represents an overlap with respect to the succeeding reaction period, it is timed by observation of the temperature so as to permit uniformity of operation through successive stages of an extended experiment. The stream of nitrogen is continued for 30 minutes to assure transfer of carbon dioxide completely to receivers E and E′, which are then weighed. The reaction vessel A and its contents are weighed to ascertain any loss of volatile material other than carbon dioxide (total loss minus carbon dioxide determined). Portions of the cool reaction mixture are analyzed for products and/or reactants as outlined earlier. If reaction is to be continued through a further interval, the reaction flask and receivers are reattached to the train and the described procedure is repeated. For each set of conditions the alkylated products were identified: *N-benzylpiperidine* as *picrate*, m.p 178° (52) and *N-cyclohexylpiperidine* as *methiodide*, m.p. 248–249° (29).

Individual experiments. The capacities of the apparatus and the nature of the manipulations made it convenient to operate generally on a 0.1 molar basis. To avoid frequent repetitions below it is entered here that 0.1 molar weights of the compounds named are as follows: benzaldehyde, 10.61 g.; cyclohexanone, 9.81 g.; piperidine, 8.51 g. For formic acid the 0.25 molar amounts most frequently used are: 88%, 13.05 g.; 98%, 11.75 g.; 99%, 11.50 g. Other quantities of reactants are indicated fully as usual.

Piperidine hydrochloride and benzaldehyde. In this experiment, under the conditions of the Plöchl-Eschweiler reaction, a solution of 6.08 g. (0.05 mole) of piperidine hydrochloride and 26.60 g. (0.25 mole) of benzaldehyde in 25 ml. of 95% alcohol was heated on a steam-bath for 30 hours. No benzylpiperidine was isolated by the procedure outlined above.

Determination of stoichiometric relationships. Sections (*a*) and (*b*). In two series of experiments the reactants were 0.1 mole of benzaldehyde or cyclohexanone, 0.1 mole of piperidine, and 0.25 mole of 88% or 98% formic acid, all previously chilled, and mixed in the order named. Upon mixing benzaldehyde and piperidine some solid benzylidene-*bis*-piperidine separated; it dissolved upon addition of formic acid. The reaction with benzaldehyde was run at 114–117°, and that with cyclohexanone at 114–118°. Data for intervals of 0.5, 1.0, 3.0, and 5.0 hours are presented in Table I. The yield of *benzylpiperidine* in 15 minutes was 59.5%. Time-yield data are represented by curves I and II in Figure 1.

Influence of acylation of amine. Section (*c*). For the preparation of benzylpiperidine the reactants were N-formylpiperidine (11.31 g.; 0.1 mole), benzaldehyde (0.1 mole), and 98% formic acid (7.83 g.; 0.15 mole). Reactions at 125–128° gave yields of 2.8% in 0.5 hour, 6.5% in 1.0 hour, 26.5% in 3.0 hours, and 43.1% in 5.0 hours. These results are represented by curve III in Figure 1. By the use of acetylpiperidine (12.71 g.; 0.1 mole), benzaldehyde (0.1 mole) and 88% formic acid (0.25 mole), reaction at 125° for 3.0 hours produced 7.9% of benzylpiperidine.

For the preparation of cyclohexylpiperidine the reactants were cyclohexanone (0.1 mole), formylpiperidine (11.31 g.; 0.1 mole) and 98% formic acid (7.05 g.; 0.15 mole). The yield in three hours at 136–138° was 14.4%.

Influence of water. Section (*d*). In each of four experiments piperidine (0.1 mole) was treated with 0.25 mole of formic acid of, respectively, 70%, 88%, 98% or 99% concentration, followed by 0.1 mole of benzaldehyde. Stratification occurred in the reaction with 70% acid. Reaction temperatures and 3-hour yields appear in Table II. Two similar experiments, using 99% formic acid and 12 g. of finely ground Drierite in one, and 12 g. of Indicating Drierite in the other, were performed in reaction vessel A′ (Figure 3). Reaction temperatires and 3-hour yields are given in Table II. In each of three experiments piperidine (0.1 mole) was treated with 0.25 mole of formic acid of, respectively, 70%, 88% or 98% concentration, followed by 0.1 mole of cyclohexanone. Data for these experiments appear in Table II. In an experiment to test the utility of N-formylpiperidine as a dehydrating agent piperidine (0.1 mole) was treated with 0.1 mole of 98% formic acid (4.70 g.), followed by 11.32 g. (0.1 mole) of N-formylpiperidine and then 0.1 mole of cyclohexanone. Reaction at 114° for 3.0 hours produced 66.7% of cyclohexylpiperidine.

Influence of the amount of formic acid. Section (*e*). In each of three experiments 0.1 mole of piperidine was treated with 98% formic acid in one of these amounts: 0.1 mole (4.70

g.), 0.25 mole (11.75 g.), 0.5 mole (23.50 g.). Benzaldehyde (0.1 mole) was added and the experiments were run at the temperatures, and with the results, given in Tables III and IV. In a second series of three experiments cyclohexanone (0.1 mole) was used instead of benzaldehyde.

Effect of excess piperidine. Section (*e*). Piperidine (17.02 g.; 0.2 mole) was treated with 98% formic acid (0.1 mole), followed by benzaldehyde (0.1 mole). Reaction at 104–114° for 3 hours produced 72.1% of benzylpiperidine.

Effect of excess piperidine formate. Section (*f*). Piperidine (17.02 g.; 0.2 mole) was treated with 98% formic acid (0.25 mole), followed by benzaldehyde (0.1 mole), and the reaction was run at 112°. In a similar experiment cyclohexanone (0.1 mole) was used instead of benzaldehyde; reaction temperature was 114–116°. The 3-hour yields appear in Table IV.

Benzylidene-bis-piperidine and formic acid. Section (*f*). Benzylidene-*bis*-piperidine (12.92 g.; 0.050 mole) was added slowly to 0.25 mole of chilled 98% formic acid. Solution occurred with slight gas evolution. When the mixture was removed from the ice-bath and allowed to come to room temperature gas evolution became vigorous and the reaction developed sensible heat. Active evolution of carbon dioxide continued without applied heat for about 20 minutes and then subsided. Analysis of an aliquot of the mixture at this stage showed that over 75% of benzylpiperidine was present; the reaction was continued at a temperature of 135° for 3 hours. The yield of benzylpiperidine was quantitative.

SUMMARY

Results of a semiquantitative study of the formation of N-benzylpiperidine and N-cyclohexylpiperidine by the Wallach alkylation reaction and by experimental modifications thereof lead to the following conclusions.

1. The reactants (amine, carbonyl compound, and formic acid) and the products (carbon dioxide and alkylated amine) are involved in equivalent amounts.[16]

2. Formylation of amine retards but does not prevent alkylation. The reactions studied are characterized by a rapid initial phase which is absent when formylpiperidine is used instead of piperidine. It is inferred that formylamine is not involved in the normal alkylation sequence.

3. The initial reaction appears to be the condensation of amine and carbonyl compound, for alkylation is promoted by conditions which favor condensation and is impeded by conditions which hinder it. Treatment of benzylidene-*bis*-piperidine, the preformed condensation product of benzaldehyde and piperidine, with formic acid led to rapid alkylation and a quantitative yield of benzylpiperidine.

4. Formic acid functions chiefly as an aldehyde and appears to be the sole operative reducing agent in the reaction.[16] The acid character of formic acid is helpful to the extent that acid catalysis is involved, and perhaps as a solvent, but is otherwise obstructive.

5. The course of the Wallach alkylation is represented to involve hydrogenation of the condensation product of amine and carbonyl compound by formic acid, either through an intermediate carbenium-ammonium formate [essentially identical with the ester intermediate previously suggested (9)] or by a hydrogen-

[16] This is not true of methylations by formaldehyde and formic acid, in which reduction is affected jointly by both compounds.

ation-dehydrogenation reaction of the Cannizzaro type. It is believed that the Wallach and Leuckart reactions involve the same essential steps.

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[Contribution from the Chemical Laboratories of New York University, St. John's University, and Lafayette College]

UNSYMMETRICAL MORPHOLINIUM AND THIAMORPHOLINIUM ALKYL SULFATES[1]

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INTRODUCTION

Systematic studies in "Symmetrical Morpholinium Alkyl Sulfates" by Niederl and co-workers (1) have now been extended to the reaction of tertiary aminse with unsymmetrical dialkyl sulfates.

The tertiary amines used in this investigation were N-substituted morpholines such as N-*n*-dodecyl-, N-*n*-tetradecyl-, N-*n*-hexadecyl-, and N-*n*-octadecylmorpholine and the corresponding N-alkylated thiamorpholines, thiamorpholine oxides, and thiamorpholine dioxides previously described by Hart and Niederl (2). The unsymmetrical dialkyl sulfates used were methyl ethyl sulfate, methyl *n*-dodecyl sulfate, methyl *n*-tetradecyl sulfate, and methyl *n*-hexadecyl sulfate, which were prepared by the method of Bushong (3).

While the products obtained by the interaction of symmetrical dialkyl sulfates with tertiary amines needed no further elucidation as to the structure of the resulting quaternary ammonium alkyl sulfates, this was not the case when unsymmetrical dialkyl sulfates were used. It became necessary to investigate the structure of the final quaternary morpholinium alkyl sulfates in order to establish which of the two alkyl radicals of the sulfate migrated to the tertiary amino nitrogen.

By the solution of this problem as illustrated below, it was determined that the smaller alkyl radical of the unsymmetrical dialkyl sulfate migrates to the nitrogen of the tertiary amine.

$$O(CH_2CH_2)_2N(CH_3) + C_{16}H_{33}OSO_2OC_{16}H_{33} \longrightarrow [O(CH_2CH_2)_2N(CH_3)(C_{16}H_{33})]^+\ C_{16}H_{33}OSO_2O^- \quad \text{m.p. } 99.5°$$

$$CH_3OSO_2OC_{16}H_{33} + O(CH_2CH_2)_2NC_{16}H_{33} \longrightarrow [O(CH_2CH_2)_2N(CH_3)(C_{16}H_{33})]^+\ C_{16}H_{33}OSO_2O^- \quad \text{m.p. } 99.5°$$

$$O(CH_2CH_2)_2N(CH_3) + CH_3OSO_2OC_{16}H_{33} \longrightarrow [O(CH_2CH_2)_2N(CH_3)_2]^+\ C_{16}H_{33}OSO_2O^- \quad \text{m.p. } 96°$$

$$O(CH_2CH_2)_2NC_{16}H_{33} + CH_3OSO_2OCH_3 \longrightarrow [O(CH_2CH_2)_2N(CH_3)(C_{16}H_{33})]^+\ CH_3OSO_2O^- \quad \text{m.p. } 68°$$

N-Methylmorpholine when reacted with di-*n*-hexadecyl sulfate yielded the same product as when N-*n*-hexadecylmorpholine was treated with methyl *n*-hexadecyl sulfate, while reaction of N-*n*-hexadecylmorpholine with dimethyl sulfate and N-methylmorpholine with methyl *n*-hexadecyl sulfate produced altogether different products.

It may also be pointed out that the use of unsymmetrical dialkyl sulfates not

[1] Presented before the Division of Organic Chemistry at the Chicago meeting of the American Chemical Society, April 1948.

only makes it possible to produce quaternary ammonium compounds in which the cation is larger than the anion, as is usual, but also makes readily accessible those in which the cation and anion are equal ("equionics"), or those in which the cation is smaller than the anion.

TABLE I

UNSYMMETRICAL DIALKYL SULFATES

COMPOUND	EMP. FORMULA	M.P. (B.P.), °C	YIELD %	%S Calc'd	%S Found
Methyl ethyl sulfate	$C_3H_8O_4S$	(100–102/45 mm.)	15	22.87	22.84
Methyl *n*-dodecyl sulfate.......	$C_{13}H_{28}O_4S$	47	35	11.43	11.39
Methyl *n*-tetradecyl sulfate.. .	$C_{15}H_{32}O_4S$	54	15	10.39	10.34
Methyl *n*-hexadecyl sulfate.....	$C_{17}H_{36}O_4S$	61	20	9.52	9.49

TABLE II

UNSYMMETRICAL N-ALKYL-N-METHYLMORPHOLINIUM ALKYL SULFATES

$[O(CH_2CH_2)_2N(CH_3)(R)]^+ \ OSO_2OR'^-$

R	R'	EMP. FORMULA	M.P. (°C)	% NITROGEN Calc'd	% NITROGEN Found
n-Hexadecyl	Ethyl	$C_{23}H_{49}NO_5S$	45	3.10	3.05
Methyl	*n*-Dodecyl	$C_{18}H_{39}NO_5S$	60	3.67	3.64
n-Dodecyl	*n*-Dodecyl	$C_{29}H_{61}NO_5S$	87	2.61	2.68
n-Tetradecyl	*n*-Dodecyl	$C_{31}H_{65}NO_5S$	80	2.48	2.42
n-Hexadecyl	*n*-Dodecyl	$C_{33}H_{69}NO_5S$	88	2.37	2.31
Methyl	*n*-Tetradecyl	$C_{20}H_{43}NO_5S$	98	3.42	3.46
n-Dodecyl	*n*-Tetradecyl	$C_{31}H_{65}NO_5S$	58	2.48	2.44
n-Tetradecyl	*n*-Tetradecyl	$C_{33}H_{69}NO_5S$	78	2.37	2.36
n-Hexadecyl	*n*-Tetradecyl	$C_{35}H_{73}NO_5S$	75	2.26	2.28
Methyl	*n*-Hexadecyl	$C_{22}H_{47}NO_5S$	96	3.20	3.15
n-Dodecyl	*n*-Hexadecyl	$C_{33}H_{69}NO_5S$	92	2.37	2.37
n-Tetradecyl	*n*-Hexadecyl	$C_{35}H_{73}NO_5S$	82	2.26	2.30
n-Hexadecyl	*n*-Hexadecyl	$C_{37}H_{77}NO_5S$	99	2.16	2.11

EXPERIMENTAL

Unsymmetrical dialkyl sulfates. The methyl ethyl, methyl *n*-dodecyl, methyl *n*-tetradecyl, and methyl *n*-hexadecyl sulfates were prepared by slight modifications of the method of Bushong (3). Of these compounds, only the first has been previously described (4, 5, 6). In each case the chlorosulfonate of the higher alcohol was prepared and reacted with sodium methoxide in anhydrous ether at low temperature. The methyl ethyl sulfate was purified by distillation *in vacuo*, the others by crystallization from ether.

Unsymmetrical N-alkyl-N-methylmorpholinium alkyl sulfates. These compounds were prepared by reacting equivalent quantities (from 0.003 to .01 mole) of the N-alkylmorpholine and the appropriate unsymmetrical dialkyl sulfate, without solvent, at 115° for six hours in a tightly stoppered Pyrex test tube heated in an oil-bath. The reaction mixture was then allowed to remain overnight at room temperature. The resultant waxy product was washed with 3 cc. of ether at 33°, cooled, and centrifuged. The ether layer containing

the more soluble unreacted starting materials was decanted. The washed product was recrystallized three times from ethyl acetate, and dried on a porous tile. In cases where there was evidence of spontaneous exothermic reaction the heating was limited to 50° for three hours. The yields for this group of compounds varied from 32–45%.

Unsymmetrical N-alkyl-N-methylthiamorpholinium alkyl sulfates. Equivalent quantities (approximately 0.003 mole) of the N-alkyl thiamorpholine, oxide, or dioxide and di-*n*-hexadecyl sulfate were added to 5 cc. of toluene which had been dried over sodium. The solution was refluxed for four hours, using an oil-bath, with an external temperature of 160–170°. Lower temperatures were found to give incomplete reaction. The toluene was distilled off *in vacuo*, a little alcohol was added, and distilled *in vacuo* to remove the last traces of toluene. The residue was taken up in ethyl acetate and crystallized from this solvent.

TABLE III

UNSYMMETRICAL N-ALKYL-N-METHYLTHIAMORPHOLINIUM ALKYL SULFATES

R	R′	EMP. FORMULA	M.P. (°C)	% NITROGEN	
				Calc'd	Found
THIAMORPHOLINIUM $[S(CH_2CH_2)_2N(CH_3)(R)]^+ \ OSO_2OR'^-$					
n-Dodecyl	*n*-Hexadecyl	$C_{33}H_{69}NO_4S_2$	76	2.30	2.28
n-Tetradecyl	*n*-Hexadecyl	$C_{35}H_{73}NO_4S_2$	112	2.20	2.23
n-Hexadecyl	*n*-Hexadecyl	$C_{37}H_{77}NO_4S_2$	92	2.10	2.13
n-Octadecyl	*n*-Hexadecyl	$C_{39}H_{81}NO_4S_2$	98	2.02	2.00
THIAMORPHOLINIUM-1-OXIDE $[OS(CH_2CH_2)_2N(CH_3)(R)]^+ \ OSO_2OR'^-$					
n-Dodecyl	*n*-Hexadecyl	$C_{33}H_{69}NO_5S_2$	127	2.24	2.21
n-Tetradecyl	*n*-Hexadecyl	$C_{35}H_{73}NO_5S_2$	128	2.14	2.12
n-Hexadecyl	*n*-Hexadecyl	$C_{37}H_{77}NO_5S_2$	110	2.05	2.04
n-Octadecyl	*n*-Hexadecyl	$C_{39}H_{81}NO_5S_2$	105	1.97	1.93
THIAMORPHOLINIUM-1-DIOXIDE $[O_2S(CH_2CH_2)_2N(CH_3)(R)]^+ \ OSO_2OR'^-$					
n-Dodecyl	*n*-Hexadecyl	$C_{33}H_{69}NO_6S_2$	130	2.18	2.16
n-Tetradecyl	*n*-Hexadecyl	$C_{35}H_{73}NO_6S_2$	88	2.09	2.07
n-Hexadecyl	*n*-Hexadecyl	$C_{37}H_{77}NO_6S_2$	105	2.01	2.03
n-Octadecyl	*n*-Hexadecyl	$C_{39}H_{81}NO_6S_2$	98	1.93	1.90

In cases where decolorization was necessary, this was done with Darco in alcohol solution. The compounds were finally recrystallized twice from acetone, and twice from ethyl acetate, or from an ethyl acetate–alcohol mixture. The melting points were taken on a Fisher-Johns electrical melting-point apparatus, and the point of complete liquefication determined.

SUMMARY

Work in the field of quaternary morpholinium and thiamorpholinium types of "invert soaps" has been extended to include the preparation of two series of unsymmetrical N,N-dialkyl-morpholinium and -thiamorpholinium alkyl sulfates possessing a balance between the carbon atom content of the anion and cation (equionics).

It has been established that, in the N-alkylation of tertiary amines by unsym-

metrical dialkyl sulfates, the smaller alkyl group migrates to the nitrogen of the tertiary amine.

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STUDIES IN THE ACRIDINE SERIES. VI. THE REACTION OF CERTAIN 9-FORMYLACRIDINES WITH 3-DI-*n*-BUTYL-AMINOPROPYLMAGNESIUM CHLORIDE

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A recent communication (1) from this Laboratory reported the synthesis of a number of acridine amino carbinols, of which three possessed slight activity towards *Plasmodium gallinaceum* (chick infection). It was pointed out at the time that this particular group of substances constituted the first in a series of four new types of acridine amino alcohols prepared for plasmodicidal study. The present paper is concerned with a group of compounds derived from various 9-formylacridines.

Amino alcohols which have proved effective plasmodicides are characterized by a secondary carbinol situated between an aromatic or heterocyclic nucleus and an aliphatic or reduced heterocyclic system (*e.g.* quinine). The amino group occurs on the α- or β-carbon with respect to the carbinol. This type of compound is usually derived, respectively, from the corresponding α-halomethyl ketone by halogen exchange (α), or from the ketone by the Mannich reaction (β), followed by reduction of the resultant amino ketone to the carbinol.

To our knowledge acridine *meso*-amino carbinols (either the α or β type) are, at present, unknown. Since such compounds should be of interest as possible plasmodicides, we have been investigating several possible, alternate routes for their synthesis. One of the more promising methods appears to be the application of some modification of the Grignard reaction. Unfortunately compounds of the type $R_m(CH_2)_xNR_2$, where x is 1 or 2, (R_m being Li or MgX) are unavailable by the usual procedures. However, Marxer (3) has made an excellent study of the preparation of this type of compound in which x is 3 or more. The application of Marxer's technique to our problem has led to a series of three acridine amino alcohols of the butanol type in good yield.

It has been found that, in virtually any series of amino alcohols in which the substituents on the amino group are varied, if plasmodicidal activity is present in *any* member of the series, the dibutylamino homolog will also be active (4). On the basis of this generalization, this investigation has been limited to the 9-dibutylaminobutanol derivatives of three substituted acridines.

9-Methylacridine, the precursor of 9-formylacridine, was prepared from diphenylamine, acetic anhydride, and fused zinc chloride according to Porai-Koshits, *et al.* (5). We were unable to attain their yield of 70%; our average yield was 40%. 9-Methylacridine condensed readily with 4-nitrosodimethylaniline either in boiling ethanol solution (2) or by fusion of the components at 115° in the presence of a little piperidine (6), to give the purported "anil" which was readily cleaved by conc'd hydrochloric acid to 9-formylacridine.

Some interesting observations made in connection with the aforementioned "anil", as well as the two anils to be described later, are worthy of special note. In all three cases low carbon values ranging between 1.2 to 3.2% was the rule.

At first, these discrepancies were attributed to water of crystallization, a view earlier entertained, but never substantiated, by Kaufmann (6). However, when no significant alteration in carbon analysis followed a 6-hour heating-period at 135°/0.3 mm., of one of the anils, we were less inclined to accept the water of crystallization idea. The answer to this dilemma was soon found in two papers by Krohnke (7) on the synthesis and reactions of nitrones. According to Krohnke, aromatic nitroso compounds are capable of interaction with reactive methylene groups in three different ways, two of which are relevant to the present problem. The usual and most common product is an azomethine or anil, which is probably formed through the intermediate $RCH_2\overset{R'}{\overset{|}{N}}OH$ as follows:

$$RCH_3 \;+\; ONR' \;\rightarrow\; \left[RCH_2\overset{R'}{\overset{|}{N}}OH\right] \;\rightarrow\; \underset{\text{(Anil)}}{R\overset{H}{\overset{|}{C}}{=}NR'} \;+\; H_2O.$$

In certain cases, however, a second or third mole of nitroso compound may react with the above intermediate oxidizing it to a *nitrone*, with the concomitant formation of an azoxy body:

$$RCH_2\overset{R'}{\overset{|}{N}}OH \;+\; 2ONR' \;\rightarrow\; \underset{\text{(Nitrone)}}{RCH{=}\overset{O}{\ddot{N}}R'} \;+\; R'\overset{O}{\ddot{N}}{=}NR' \;+\; H_2O.$$

The fact that nitrones, like their related anils, are readily hydrolyzed to the same aldehyde by mineral acids, probably accounts for the lack of interest, on the part of earlier workers, in the structure of the intermediate "anils".

Having once obtained and characterized the pure aldehydes, we considered it of interest, in view of the indeterminate nature of the precursory anils, to determine whether chemically pure anils would be formed by condensing the aldehydes with 4-aminodimethylaniline under the conditions previously employed. With all three aldehydes, the resulting anils not only proved to be chemically homogeneous, but each differed from the corresponding anil originally prepared from the 9-methyl derivative, in crystalline form, m.p., X-ray powder pattern and absorption spectrum in the visible range.

$$R\overset{H}{C}{=}\overset{O}{\ddot{N}}R' \;+\; SO_2 \;\rightarrow\; R\overset{H}{C}{=}NR'$$

We have now secured evidence which appears to support Krohnke's view regarding the N-oxide configuration for the nitrones. Just as N-oxides are reduced to the parent amine by SO_2, so treatment of our anil-nitrone mixture with SO_2 resulted in reduction of the nitrone fraction to give the homogeneous anil. The latter now not only gave correct carbon and hydrogen values but had the same crystalline form as the anil derived from 9-formylacridine; no depression in mixture melting point was observed.

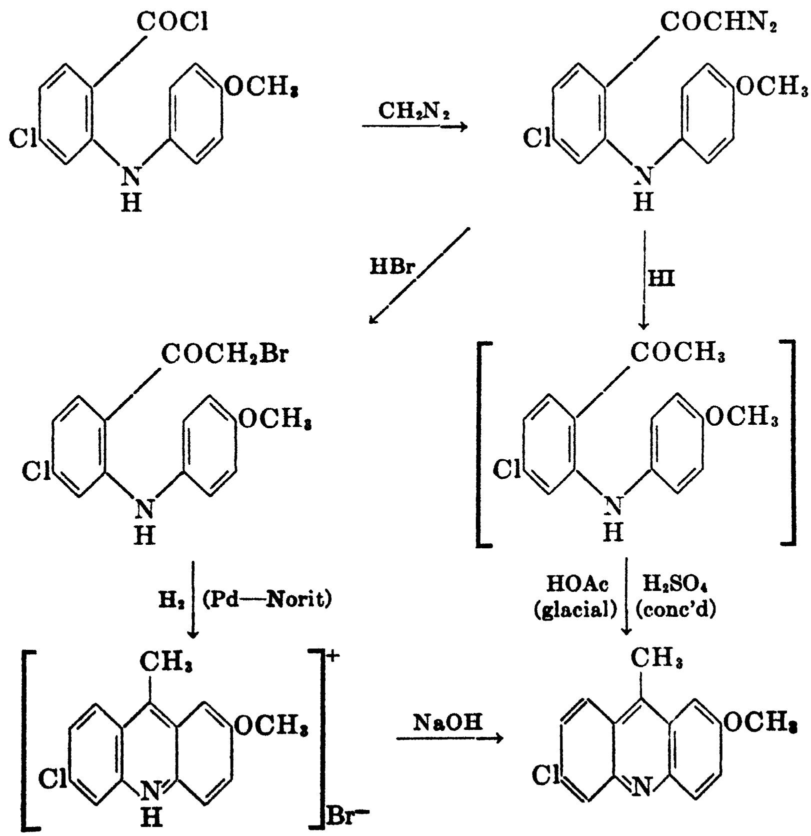
Initial attempts to prepare 2-methoxy-9-methylacridine involved the treatment of 2-methoxyacridone with methylmagnesium iodide. This approach was patterned after the work of Semon and Craig (8) who found that acridone and

methylmagnesium iodide react to give a mixture of 9-methylacridine and 9,9-dimethylacridane in approximately 2:1 ratio. 2-Methoxyacridone was found to react with methylmagnesium iodide, but the method was abandoned because of the poor yield of 2-methoxy-9-methylacridine (10–15%).

Acridone is known to react with phenyllithium to give 9-phenylacridine in 90% yield (9). We were unable, however, to isolate any 2-methoxy-9-methylacridine from the reaction of 2-methoxyacridone with methyllithium under a variety of conditions.

The method ultimately adopted for the large scale preparation of 2-methoxy-9-methylacridine consisted of condensing *o*-aminoacetophenone (10) with 4-bromoanisole followed by cyclization of the resulting substituted diphenylamine according to Jensen (11). The 2-methoxy anil or, more properly, "anil–nitrone" mixture, prepared by fusion of 2-methoxy-9-methylacridine with 4-nitrosodimethylaniline afforded the desired aldehyde on hydrolysis with conc'd hydrochloric acid.

The method of Jensen (11) proved superior, too, for the synthesis of 2-methoxy-6-chloro-9-methylacridine from 2-amino-4-chloroacetophenone (10) and 4-bromoanisole. The same acridine derivative was obtained in two other ways, albeit in low yield, from N-(4′-methoxyphenyl)-4-chloroanthraniloyl chloride (12) according to the following sequence of reactions:



The concomitant dehydrobromination of the bromoketone and cyclization of the intermediate to the substituted 9-methylacridine is noteworthy, despite the low yield obtained.

Fusion of 2-methoxy-6-chloro-9-methylacridine with 4-nitrosodimethylaniline followed by acid hydrolysis of the intermediate "anil–nitrone" mixture afforded the desired aldehyde.

The three drugs described here exhibited strong plasmodicidal activity towards *P. gallinaceum* (chick infection). The respective quinine equivalents were: 0.3 for the unsubstituted acridine amino butanol; 0.5 for the 2-methoxy homolog, and 0.8 for the 2-methoxy-6-chloro homolog (13).

Acknowledgment. The microanalyses are by C. A. Kinser and Betty Mount, both formerly of this Laboratory.

EXPERIMENTAL

Melting points are uncorrected.

9-Methylacridine. The synthesis of this substance from diphenylamine, acetic anhydride, and fused zinc chloride was effected according to Porai-Koshits (5). 9-Methylacridine may also be prepared from *o*-aminoacetophenone and bromobenzene (10, 11).

α-9-Acridyl-N-(4-dimethylaminophenyl)nitrone. (*From 9-methylacridine*). Eisleb's directions (2) for condensing 9-methylacridine with 4-nitrosodimethylaniline in ethanol solution afforded the anil–nitrone mixture in 66% yield. After two crystallizations from ethanol, dark red prisms, m.p. 247–248° (d).

Anal. Calc'd for $C_{22}H_{19}N_3O$: C, 77.4; H, 5.61; N, 12.31.
Found: C, 78.4, 78.3, 78.5, 78.04, 78.13.
H, 5.87, 5.99, 5.85, 6.02, 5.91; N, 11.93.

The constancy of the above analytical values suggests the formation of a double compound consisting of 3 moles of nitrone and 1 mole of anil. This discrepancy in the analysis of nitrones has been noted previously (7)[1].

Another route to the nitrone lies in the fusion of the components at 115° in the presence of a trace of piperidine (6).

9-Formylacridine. The acid hydrolysis of the above nitrone to the aldehyde was effected in 75% yield according to Eisleb (2). Crystallization from methanol–water gave golden-yellow needles, m.p. 149.5–151°.

9-(4-Dimethylaminophenyliminomethyl)acridine. (*From 9-formylacridine*). A mixture of 0.5 g. of acridine-9-aldehyde, 0.35 g. (1.1 equiv.) of *p*-aminodimethylaniline,[2] and 2 drops of piperidine was heated at 115–120° (oil-bath) for 30 minutes. The dark melt was triturated with a few ml. of cold ethanol, diluted with ether, and filtered; yield 0.45 g. The *anil* crystallized in garnet rhombs from ethanol. After three crystallizations, m.p. 257.5–259°.

Anal. Calc'd for $C_{22}H_{19}N_3$: C, 81.2; H, 5.89.
Found: C, 81.2; H, 6.04.

Regeneration of the aldehyde. A small amount of the above anil was hydrolyzed with dilute HCl in the usual way and the product crystallized from methanol-water; bright yellow needles, m.p. 149–150°, alone or in mixture with 9-formylacridine.

Reduction of the nitrone to the anil. A cooled suspension of 0.5 g. of nitrone in 25 ml. of anhydrous tetrahydrofuran was treated with 25 ml. of a cold, saturated solution of dry

[1] Since the submission of our communication, the paper of Chardonnens and Heinrich, *Helv. Chim. Acta*, **32**, 656 (1949), appeared, in which this *nitrone*, after recrystallization from chlorobenzene, gave a correct analysis. The reported m. p. was 243° as compared with our m. p. of 247–248°.

[2] Prepared by high-pressure reduction (135 atms.) of 4-nitrosodimethylaniline over Raney nickel at room temperature.

sulfur dioxide in tetrahydrofuran. After standing for 15 hours (at 20°), with the exclusion of moisture, the solution was filtered from a small amount of solid material, concentrated to *ca.* 10 ml. and basified with excess 2.5 *N* Na_2CO_3 solution. The resultant precipitate was washed with water and dried (0.36 g.). Recrystallization from ethanol afforded 0.11 g. of garnet rhombs, m.p. 255–257°. A mixture m.p. with the pure *anil* (derived from 9-formylacridine) showed no depression.

Anal. Calc'd for $C_{22}H_{19}N_3$: C, 81.2; H, 5.89.

Found: C, 81.2; H, 6.09.

3-Di-n-butylaminopropylmagnesium chloride. This preparation is a modification of the excellent general procedure developed by Marxer for preparing this and other amino Grignard reagents (3). It is essential that the apparatus and solvents used be absolutely dry. While some moisture may be tolerated once the reaction between the amino halide and the magnesium has been initiated, the presence of moisture at the outset makes it quite difficult to start the reaction. If the apparatus is not disassembled, but is only opened to the extent necessary to remove the Grignard reagent at the end of the reaction, the subsequent preparation of a new batch is much facilitated. The ether used as solvent in the first phase of the reaction should be dried with a Grignard reagent, such as EtMgBr, and distilled directly into the reaction flask. The use of an inert atmosphere is recommended and we have successfully employed dry hydrogen or helium; nitrogen is somewhat less suitable.

Ethyl (or methyl) halide is used to activate the magnesium. In small runs it may be desirable to remove most of this alkylmagnesium halide and this may be accomplished if a stopcock is sealed into the bottom of the flask. In larger runs, this small amount of extraneous RMgX is usually inconsequential.

It is important to keep the reaction going continuously. This is best accomplished by using a minimum of ether, adding the halide as rapidly as possible, and employing an ether-benzene solvent mixture (the latter seems to prevent the formation of a surface coating on the magnesium).

The following is a *typical run*: 60 g. of magnesium turnings was covered with dry ether and activated by the addition of 3 ml. of ethyl bromide. As soon as the reaction had subsided, another ml. of ethyl bromide was added and, as this reaction approached its peak, 50 ml. of 3-di-*n*-butylaminopropyl chloride was introduced during the next few minutes. When the reaction was well under way, a solution of 224 g. of 3-di-*n*-butylaminopropyl chloride in a mixture of 125 ml. of dry ether and 250 ml. of dry benzene was added at the rate of 15 ml. per minute. At the end of the spontaneous reaction, the solution was refluxed for 30 minutes, separated from excess magnesium and diluted to one liter. Typical electrometric titration values indicated the solution to be 0.82 *molar* with respect to magnesium and 1.09 *molar* in amine. This represented a yield of 70% of amino Grignard reagent and 100% recovery of amine.

9-(4-Di-n-butylamino-1-hydroxybutyl)acridine. A stirred solution of 6.8 g. (0.0328 mole) of 9-formylacridine in 250 ml. of dry benzene was gradually treated with 90 ml. (0.0738 mole) of a warm 0.82 *M* solution of 3-di-*n*-butylaminopropylmagnesium chloride in benzene. After refluxing for 15 mins. the Michler's ketone test was only faintly positive. The complex was decomposed with aqueous NH_4Cl, the organic layer separated and thoroughly extracted with 1.0 *N* HCl. Upon basifying with NH_4OH, an oil separated which soon crystallized, m.p. 98–103°; yield 10 g. After three recrystallizations from 70% ethanol, from which the base separates in stout prisms, the m.p. was 96–102°; yield 5.9 g. The substance apparently contains one mole of water of crystallization which is easily lost by drying in a vacuum-desiccator. The base becomes gummy and resolidifies as the hydrate when exposed to the atmosphere.

Anal. Calc'd for $C_{25}H_{34}N_2O \cdot H_2O$: C, 75.7; H, 9.15.

Found: C, 75.9; H, 9.26.

The *dihydrochloride*, prepared in acetone with the calculated amount of conc'd HCl, crystallized in bright-yellow needle rosettes from absol. ethanol; m.p. 168–170° d.

Anal. Calc'd for $C_{25}H_{36}Cl_2N_2O$: C, 66.5; H, 8.04.
Found: C, 66.2; H, 7.90.

2-Methoxy-9-methylacridine. A stirred mixture of 26 g. (0.192 mole) of *o*-aminoacetophenone (10), 43.5 g. (0.23 mole) of redistilled *p*-bromoanisole, 43 g. (0.405 mole) of anhydrous Na_2CO_3 (dried at 120°), 1.55 g. of copper powder, and 200 ml. of dry nitrobenzene was gradually heated to 185° (oil-bath temp.) where slight foaming occurred. The temperature was cautiously raised to 205–210°; excessive foaming being effectively controlled by intermittent withdrawal of the source of heat. After 3 hours heating the nitrobenzene and excess bromoanisole were steam-distilled off, the residual oil taken up in ether, dried and concentrated (*vacuo*); the yield was 42 g. This oil was cyclized by dissolving it in 105 ml. of glacial acetic acid, carefully treating with 21 ml. of conc'd H_2SO_4 and heating on the steam-bath for 6 minutes. The crystalline acridine salt which separated as a thick sludge was cooled and dispersed in 500 ml. of ice-cold water. The cooled suspension was basified (conc'd NH_4OH) and the dark brown precipitate washed with water and dried; yield 33 g. Although the procedure was slow, the product was best purified by sublimation at 140–145°/0.4 mm. In order to prevent caking, it was found advantageous to mix the crude material with a little clean sand before sublimation. Yield, 17.7 g. (44%, based on *o*-aminoacetophenone used). Recrystallization from ether–petroleum ether (30–60°) afforded 15.3 g. of pale yellow needles. An analytical sample was sublimed twice again, m.p. 140–141.5°.

Anal. Calc'd for $C_{15}H_{13}NO$: C, 80.7; H, 5.87.
Found: C, 80.9; H, 5.88.

α-(2-Methoxy-9-acridyl)-N-(4-dimethylaminophenyl)nitrone. (*From 2-methoxy-9-methylacridine*). An intimate mixture of 8 g. (0.0358 mole)of 2-methoxy-9-methylacridine, 10.8 g. (0.072 mole) of *p*-nitrosodimethylaniline, and 6 drops of piperidine was gradually heated to 95° (oil-bath). When the initial exothermic reaction subsided, the temperature was raised and maintained at 120° for 30 minutes. The cooled melt was triturated with 10 ml. of ethanol, diluted with 150 ml. of ether, and filtered; yield 10.8 g. (82%). From ethanol (Norit), long, yellow rectangular plates; after four crystallizations, m.p. 225–227° dec. The analytical sample was dried for 2 hours at 97° (*in vacuo*).

Anal. Calc'd for $C_{23}H_{21}N_3O_2$: C, 74.37; H, 5.70.
Found: C, 74.6; H, 5.69.

2-Methoxy-9-formylacridine. A suspension of 12 g. of the above nitrone in a mixture of 22 ml. of conc'd HCl and 38 ml. of water was heated on the steam-bath for 10 minutes. The resulting crystalline, orange magma of the formylacridine hydrochloride was washed with 125 ml. of cold (1:3) saturated NaCl-2 *N* HCl mixture. Digestion of the hydrochloride with a concentrated aqueous solution of sodium acetate (5 minutes at 100°) afforded the crude aldehyde. A clarified (Norit) solution of the latter in 350 ml. of methanol was concentrated to *ca.* 150 ml. and diluted with an equal volume of water. The bright yellow precipitate weighed 4.5 g. (57%), m.p. 145–147°. It was purified by sublimation at 145°/0.4 mm., yellow prisms, m.p. 146.5–148°.

Anal. Calc'd for $C_{15}H_{11}NO_2$: C, 75.9, H, 4.67.
Found: C, 76.2; H, 4.86.

The *oxime*, prepared in the usual way, crystallized in yellow needles (ethanol), m.p. 236–238° dec.

Anal. Calc'd for $C_{15}H_{12}N_2O_2$: C, 71.4; H, 4.80.
Found: C, 71.5; H, 5.07.

2-Methoxy-9-(4-dimethylaminophenyliminomethyl)acridine. (*From 2-methoxy-9-formylacridine*). The condensation of 0.5 g. of 2-methoxy-9-formylacridine with 0.35 g. (1.2 equiv.) of *p*-aminodimethylaniline using 2 drops of piperidine as catalyst was carried out as outlined above. Recrystallization of the crude anil (0.42 g.) from ethanol (Norit) afforded amber plates mixed with a small quantity of bright red needles. Mechanically separated, the amber plates showed the m.p. 184–185.5°, while the red needles melted at 183.5–185°; on mixing the two, the m.p. was 184–185.5°. Although the two crystalline

modifications are readily interconvertible, the red needles appear to be more stable since repeated recrystallization of a mixture gradually leads to the red-needle form exclusively. A mixture of either crystalline form with the anil derived from 2-methoxy-9-methylacridine (m.p. 225–227° dec.) melted at 177.5–179° dec.

Three recrystallizations from ethanol did not raise the m.p. (183.5–185°) of the *red-needle form*.

Anal. Calc'd for: $C_{23}H_{21}N_3O$: C, 77.7; H, 5.96.
Found: C, 77.8; H, 6.19.

Hydrolysis of a small amount of the crude 2-methoxy anil with dil. HCl afforded a bright yellow substance, m.p. 147–148°, identical with 2-methoxy-9-formylacridine.

2-Methoxy-9-(4-di-n-butylamino-1-hydroxybutyl)acridine. One hundred fifty-five ml. (0.127 mole) of 0.82 *M* 3-di-n-butylaminopropylmagnesium chloride in benzene was gradually added to a stirred benzene solution of 6.7 g. (0.0283 mole) of 2-methoxy-9-formylacridine. The reaction mixture was refluxed for 15 minutes and then worked up as described above. The resulting gummy base was conveniently purified by dissolving it in a little absolute ethanol and adding a solution of 20 g. (excess) of 85% phosphoric acid in 80 ml. of absolute ethanol. The sparingly soluble phosphate that separated was thoroughly washed with absolute ethanol, dried, and converted to the free base (NH_4OH–ether); yield 8.8 g., m.p. 95–105°. The latter crystallized in thick prisms from ethanol, 6.8 g., m.p. 103.6–105°. Two further recrystallizations gave m.p. 105–6°.

Anal. Calc'd for $C_{26}H_{36}N_2O_2$: C, 76.4; H, 8.88.
Found: C, 76.6; H, 8.94.

The *dihydrochloride*, prepared in acetone with conc'd HCl, crystallized in yellow needles from absol. ethanol–ether; m.p. 179–180.5° d.

Anal. Calc'd for: $C_{26}H_{38}Cl_2N_2O_2$: C, 64.8; H, 7.96.
Found: C, 64.4; H, 7.82.

The compound formed with *perchloric acid* sintered at 98° and melted at 181–3° (aq. ethanol); the compound formed with *phosphoric acid* crystallized as small rosettes from aqueous ethanol.

2-Nitro-4-chloroacetophenone was prepared according to the method of Leonard and Boyd (10). The final product, obtained in 72% yield (lit. 61%), melted at 54–56°; 10° higher than that reported (10).

The *oxime* crystallized in white needles from aqueous ethanol; m.p. 95°.

Anal. Calc'd for $C_8H_7ClN_2O_3$: C, 44.8; H, 3.29.
Found: C, 45.0; H, 3.33.

The *semicarbazone*, cream colored, hair-like needles or stout prisms from ethanol; m.p. 229–231° (sinters at 224°).

Anal. Calc'd for $C_9H_9ClN_4O_3$: C, 42.1; H, 3.54.
Found: C, 42.2; H, 3.84.

2-Amino-4-chloroacetophenone. The selective. catalytic reduction of the nitro group in 2-nitro-4-chloroacetophenone proceeded smoothly (PtO_2–ethanol) (10).

2-Methoxy-6-chloro-9-methylacridine. A. From 2-amino-4-chloroacetophenone. The condensation of 7.8 g. (0.046 mole) of 2-amino-4-chloroacetophenone with 13 g. (0.0695 mole) of redistilled *p*-bromoanisole in 60 ml. of nitrobenzene in the presence of 13 g. of anhydrous sodium carbonate, 0.5 g. of copper powder, and 2 drops of water was carried out as previously described under 2-methoxy-9-methylacridine. The crude, oily product was cyclized with a mixture of 25 ml. of glacial acetic acid and 5 ml. of conc'd H_2SO_4 by warming on the steam-bath for 5 minutes. The resulting acridine salt was washed well with glacial acetic acid, then with ether; yield 10.7 g. The salt was best crystallized from glacial acetic acid; m.p. 220–230° dec.

The *base*, regenerated from the purified sulfate, weighed 4.3 g. (37%), m.p. 169–170°. It could be sublimed at 160°/0.4 mm.; m.p. 170°.

Anal. Calc'd for $C_{15}H_{12}ClNO$: C, 69.9; H, 4.70.
Found: C, 70.2; H, 4.79.

B. From N-(4-methoxyphenyl)-4-chloroanthraniloyl chloride. The diazoketone. To a stirred, ice-cooled, ethereal solution of diazomethane (from 3.1 g. of nitrosomethylurea), a solution of 2 g. of N-(4-methoxyphenyl)-4-chloroanthraniloyl chloride (12) in 50 ml. of dry ether was added during 20 minutes. After 12 hours at 5°, concentration (*vacuo*) at 25–35° afforded 1.9 g. of bright yellow, nacreous plates, m.p. 106–107.5° (gas evolution). A mixture of this with the original acid chloride (m.p. 108–110°) melted at 85°.

The bromoketone. A stirred solution of the diazoketone (1.9 g.) in 65 ml. of dry ether was treated, at 0°, with a mixture of 1.75 ml. (2.2 equiv.) of 48% HBr, 10 ml. of ether, and a few drops of absolute ethanol to ensure homogeneity. The ice-bath was removed and stirring continued for 45 minutes. After washing with water and dil. $NaHCO_3$, the ether solution was digested with Norit, filtered, and concentrated to a small volume. The addition of 4 volumes of petroleum ether (30–60°) and a seed crystal afforded, after 15 hours, 1.2 g. of slender orange prisms, m.p. 102–103.5°; unchanged after two more recrystallizations from ether–petroleum ether.

Anal. Calc'd for $C_{15}H_{13}BrClNO_2$: C, 50.8; H, 3.69.
Found: C, 51.1; H, 3.73.

Debromination. A solution of 1 g. of the above recrystallized bromoketone in 90 ml. of absolute ethanol was shaken in hydrogen with 0.6 g. of palladium-Norit catalyst (5% Pd); 84 ml. (1.1 moles) of H_2 was absorbed in 1 hour. Concentration (*vacuo*) yielded 0.7 g. of yellow needles mixed with a little oil. After two triturations with 3-ml. portions of cold methanol, the needles were crystallized from methanol; 0.15 g., m.p. 279–281° dec. Two more recrystallizations raised the m.p. to 281–282.5° dec.

Anal. Calc'd for $C_{15}H_{13}BrClNO$: C, 53.2; H, 3.87.
Found: C, 53.3; H, 3.66.

The oily fraction was not examined.

By suspending the crystalline fraction (finely powdered) in 2 *N* NaOH and extracting with ether, a light yellow solid was obtained, m.p. 167–169°. Sublimation at 150°/0.4 mm. gave pale yellow prisms, m.p. 170–171.5°, not depressed when mixed with 2-methoxy-6-chloro-9-methylacridine (above).

C. From N-(4-methoxyphenyl)-4-chloroanthraniloyl chloride, via the diazoketone and hydriodic acid. Employing the technique described by Wolfram (14), 6 ml. of 47% HI (by dilution of freshly distilled 57% acid) was added, all at once, to a solution of 2 g. of the above-described diazoketone in 15 ml. of chloroform. Gas evolution accompanied the ensuing, mildly exothermic reaction. After shaking for 5 minutes, a little water was added, the $CHCl_3$ layer separated and washed successively with water, sodium thiosulfate, water, and then dried. The $CHCl_3$ solution gave 1.8 g. of a dark brown syrup.

Cyclization. One and two-tenths grams of the above syrup dissolved in 4 ml. of glacial acetic acid was treated with 1 ml. of conc'd H_2SO_4 and heated on the steam-bath for 6 minutes. The dark brown solution was poured into 50 ml. of ice-water, basified with conc'd ammonia and the greenish-yellow precipitate dried (0.9 g.). A clarified (Norit) ethereal solution of the latter was concentrated to incipient crystallization. The cooled, crystalline suspension was freed of mother liquor and the yellow prisms rinsed with petroleum ether (30–60°); m.p. 164–168°. After two sublimations at 150°/0.4 mm., the m.p. was 170.5–172°. A mixture m.p. with 2-methoxy-6-chloro-9-methylacridine (see above) showed no depression.

α-(2-Methoxy-6-chloro-9-acridyl)-N-(4-dimethylaminophenyl)nitrone. (From 2-methoxy-6-chloro-9-methylacridine). An intimate mixture of 8.4 g. (0.032 mole) of 2-methoxy-6-chloro-9-methylacridine, 9.8 g. (0.065 mole) of *p*-nitrosodimethylaniline, and 8 drops of piperidine was carefully heated, with frequent stirring, in an oil-bath (115–120°) for 30 minutes. The cooled reaction product was processed as before (see 2-methoxy analog). Recrystallization of the crude material (12.5 g.) from ethanol (Norit) yielded 8.6 g. of a mixture of garnet colored prisms and dark red needles. Both forms melted at 196–198° dec.; no depression on mixture. The red needles reverted to the garnet prisms on repeated

recrystallizations; after three recrystallizations, m.p. 198–200° dec. The analytical sample was dried for 2 hours at 78°/0.4 mm.

Anal. Calc'd for $C_{23}H_{20}ClN_3O_2$: C, 68.06; H, 4.97.
Found: C, 69.7, 69.5; H, 5.18, 5.01.

2-Methoxy-6-chloro-9-formylacridine. The hydrolysis of 10.4 g. of the above nitrone with a mixture of 19 ml. of conc'd HCl and 33 ml. of water was effected as outlined under 2-methoxy-9-formylacridine. The crude aldehyde was purified by dissolving it in 125 ml. of boiling dioxane (Norit) and diluting the cooled filtrate with 2 volumes of methanol. The yellow crystals were washed with ether; 4.6 (64%), m.p. 185–186°. Yellow prisms, m.p. 185–186°, were obtained by subliming a sample at 165–170°/0.3 mm.

Anal. Calc'd for $C_{15}H_{10}ClNO_2$: C, 66.3; H, 3.71.
Found: C, 66.1; H, 3.77.

The *oxime* crystallized in yellow needles (ethanol), m.p. 240–241° dec.

Anal. Calc'd for $C_{15}H_{11}ClN_2O_2$: C, 62.8; H, 3.87.
Found: C, 63.1; H, 3.87.

2-Methoxy-6-chloro-9-(4-dimethylaminophenyliminomethyl)acridine. (*From 2-methoxy-6-chloro-9-formylacridine*). One-half gram of 2-methoxy-6-chloro-9-formylacridine was condensed at 115° with 0.3 g. (1.2 equiv.) of *p*-aminodimethylaniline in the presence of 2 drops of piperidine and the product isolated as usual. The anil (0.44 g.) crystallized from ethanol in fine, dark red needles, m.p. 196°.

Anal. Calc'd for $C_{23}H_{20}ClN_3O$: C, 70.9; H, 5.17.
Found: C, 70.9; H, 5.28.

A mixture of this anil with the nitrone obtained from 2-methoxy-6-chloro-9-methylacridine (m.p. 198–200° dec.) melted at 194–195° dec. The hydrolysis (dil. HCl) of a small amount of this anil yielded a bright yellow solid, m.p. 184–185°, not depressed by 2-methoxy-6-chloro-9-formylacridine.

2-Methoxy-6-chloro-9-(4-di-n-butylamino-1-hydroxybutyl)acridine. A stirred solution of 5 g. (0.0184 mole) of 2-methoxy-6-chloro-9-formylacridine in 130 ml. of dry benzene was treated with 48 ml. (0.0393 mole) of a warm 0.82 *N* solution of 3-di-n-butylaminopropylmagnesium chloride in benzene. The system was gently refluxed for 50 minutes, cooled and decomposed with cold aqueous NH_4Cl. The aqueous layer was extracted once with benzene and the combined benzene solutions were diluted with ether and dried over sodium sulfate. The resulting syrupy carbinol (10 g.) was cooled in ice and treated dropwise with 20% ethanolic H_3PO_4 (to Congo Red acidity); scratching induced crystallization. After 12 hours at 5° the bright yellow phosphate was washed with a little cold absolute ethanol; yield 10.2 g., m.p. 196–198° dec.

The free base, regenerated from the salt (NH_4OH–ether) appeared as an amber syrup (6.1 g.). On rubbing this with a little petroleum ether (28–38°) slow crystallization occurred. Repeated recrystallization from petroleum ether gave small, pale yellow rhombs, m.p. 87–88.5°.

Anal. Calc'd for $C_{26}H_{35}ClN_2O_2$: C, 70.5; H, 7.96.
Found: C, 70.2; H, 8.00.

The *dihydrochloride* was prepared in acetone with the calculated amount of conc'd HCl, and recrystallized from a concentrated absolute ethanol solution; minute, yellow needles, m.p. 195–197° dec.

Anal. Calc'd for $C_{26}H_{37}Cl_3N_2O_2$: C, 60.5; H, 7.23.
Found: C, 60.2; H, 7.34.

SUMMARY

1. The synthesis of three new amino carbinols possessing strong plasmodicidal activity, and derived from various 9-formylacridines is described.

2. The formation of nitrones through the condensation of aromatic nitroso compounds with reactive methylene groups has been confirmed.

3. The reduction, by sulfur dioxide, of a nitrone to the corresponding anil suggests an N-oxide configuration in the former.

4. The synthesis of two new acridine-9-aldehydes is reported.

BETHESDA 14, MD.

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[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

PREPARATION AND PROPERTIES OF DIETHYLENE GLYCOL BIS-CARBONATES OF ALKYL LACTATES[2] $O[CH_2CH_2OCOOCH(CH_3)COOR]_2$

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Recent papers (1,2) described various carbonates of lactic esters, most of which have high boiling points and the structure $ROCOOCH(CH_3)COOR'$. In extending this study of lactic acid derivatives having high boiling points[3], a series of diethylene glycol bis-(1-carbalkoxyethylcarbonates)

$$O[CH_2CH_2OCOOCH(CH_3)COOR]_2$$

I

was prepared by treating alkyl lactates with diethylene glycol *bis*-chloroformate, $O[CH_2CH_2OCOCl]_2$. These compounds are of considerable interest because of their potential value as plasticizers (4) and the ease with which they can be made from commercially available intermediates. The preparation and certain properties (Table I) of the lactate diethylene glycol *bis*-carbonates (I) are reported in this paper.

Physical properties. Straight lines (Figs. 1 and 2) resulted when the boiling points were plotted against pressure on a Cox chart (10). Straight lines were obtained also by plotting log (pressure + 0.01) against temperature.

Working with homologous series of relatively simple compounds, such as *n*-paraffins (6,11), *n*-alkanols (6,12), aliphatic monoesters (13,14), diesters (6) and ether esters (15), the authors and other workers have previously determined linear relationships between M/*d* (M, molecular weight; *d*, density), M/*n* (*n*, refractive index), T^2 (T = b.p., °K.), log p (p, vapor pressure), and log η (η, viscosity) on the one hand and molecular weight or carbon atoms (x) on the other. These relationships were applied to the homologous diethylene glycol *bis*-carbonates of *n*-alkyl lactates (Tables II and III and Figures 3 and 4) (a) to determine whether such relationships are applicable to complex compounds having several functional groups, (b) to develop equations for calculating the physical properties of the missing members of the homologous series, (c) to provide quantitative relations[4], between any one property, such as boiling point, and the other

[1] One of the Laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture.

[2] Much of the material described in this paper was included in two papers presented by one of the authors (C. E. Rehberg) before the Division of Organic Chemistry and the Division of Paint, Varnish, and Plastics Chemistry at the New York meeting of the American Chemical Society, September 1947.

[3] Many of the high-boiling lactic acid derivatives thus far prepared are useful as plasticizers (1–7).

[4] Achieved, for example, by selecting the two equations giving the relationship between boiling point and carbon atoms (x) and that between density and x, and then relating boiling point to density by eliminating x from the two equations.

TABLE I

YIELDS, ANALYSES, AND VISCOSITIES OF DIETHYLENE GLYCOL *bis*-CARBONATES OF ALKYL LACTATES

$O[CH_2CH_2OCOOCH(CH_3)COOR]_2$

ALKYL LACTATE	YIELD, %	CARBON %		HYDROGEN, %		SAPON. EQUIV.		CARBONATE AS CO_2		VISCOSITY, CENTIPOISES AT	
		Calc'd	Found	Calc'd	Found	Calc'd	Found	Calc'd	Found	20°	40°
Methyl......	[a]	45.9	46.0	6.1	6.1					1818	187.0
Ethyl..........	85	48.7	48.5	6.7	6.9	65.7	65.8	22.3	22.3	375.4	70.76
n-Propyl.......	[a]					70.6	70.6	20.8	20.6	309.8	68.61
Isopropyl.....	[a]					70.6	70.6	20.8	20.6	555.4	88.93
n-Butyl.	75	53.3	53.1	7.6	7.6					206.3	52.80
Isobutyl.......	74					75.1	75.3	19.5	20.4	482.2	87.77
sec-Butyl......	77					75.1	74.9	19.5	19.6	476.2	88.22
n-Hexyl........	93					84.4	85.5	17.4	17.2	232.1	59.83
2-Ethylbutyl...	95					84.4	84.3	17.4	17.3	327.5	75.01
n-Octyl......	97					93.8	96.4	15.6	15.9	204.5	58.60
2-Ethylhexyl...	70					93.8	93.4	15.6	15.6	307.5	73.18

[a] Technical grades of these esters, kindly supplied by Franklin Strain and associates of the Columbia Chemical Division of the Pittsburgh Plate Glass Company, were redistilled and examined by the authors.

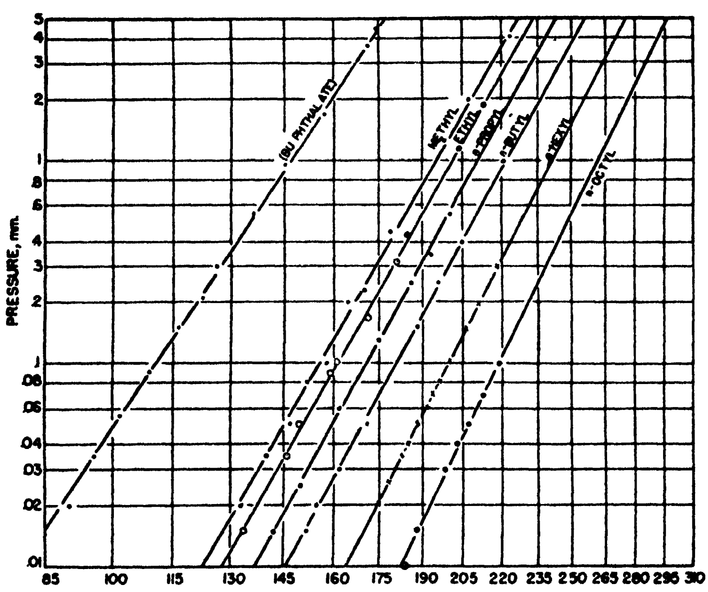

FIGURE 1. Boiling Points of Diethylene Glycol *bis*-Carbonates of Lactic Esters ($O(CH_2CH_2OCOOCH(CH_3)COOR)_2$)

properties, (that is, density, refractive index, etc.,) and (d) to provide an additional criterion of purity.

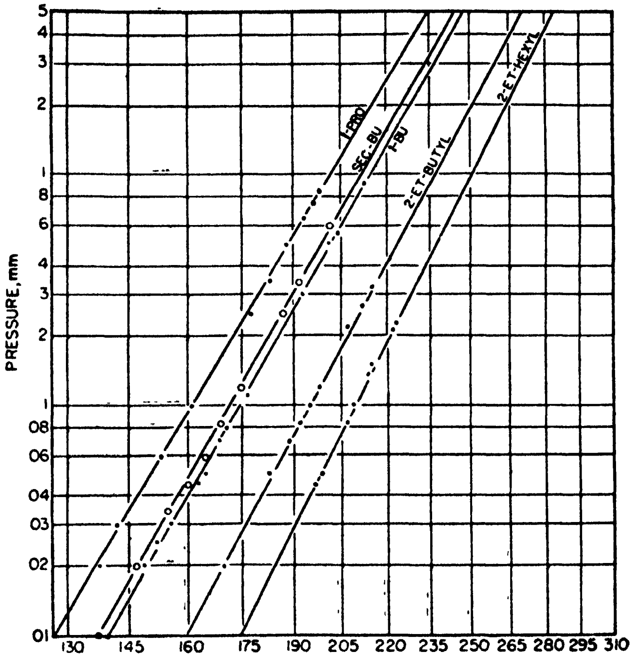

FIGURE 2. Boiling Points of Diethylene Glycol *bis*-Carbonates of Lactic Esters ($O(CH_2CH_2OCOOCH(CH_3)COOR)_2$)

TABLE II

PROPERTIES OF DIETHYLENE GLYCOL *bis*-CARBONATES OF ALKYL LACTATES

$O[CH_2CH_2OCOOCH(CH_3)COOR]_2$

LACTATE	n_D^{20}	n_D^{40}	d_D^{20}	d_D^{40}	MOLECULAR REFRACTION Calc'd	Found at 20°	Found at 40°
Methyl	1.4432	1.4366	1.2411	1.2228	78.40	78.27	78.43
Ethyl	1.4407	1.4336	1.1882	1.1690	87.63	87.59	87.78
Propyl	1.4420	1.4348	1.1539	1.1356	96.87	96.85	97.01
Isopropyl	1.4370	1.4300	1.1430	1.1232	96.87	96.81	97.14
Butyl	1.4432	1.4360	1.1270	1.1087	106.11	106.00	106.25
Isobutyl	1.4413	1.4347	1.1224	1.1045	106.11	106.04	106.37
sec-Butyl	1.4400	1.4328	1.1213	1.1046	106.11	105.90	105.95
Hexyl	1.4455	1.4387	1.0842	1.0672	124.58	124.48	124.79
2-Ethylbutyl	1.4472	1.4406	1.0919	1.0761	124.58	124.01	124.41
Octyl	1.4477	1.4409	1.0565	1.0413	143.05	142.48	142.66
2-Ethylhexyl	1.4488	1.4420	1.0580	1.0420	143.05	142.58	142.89

Although the relationships used earlier with simpler homologous compounds were applicable for the boiling points, vapor pressures, densities, and refractive indices of the diethylene glycol *bis*-carbonates of *n*-alkyl lactates (Table III),

TABLE III

EQUATIONS RELATING PHYSICAL CONSTANTS OF $O[CH_2CH_2OCOOCH(CH_3)COOR]_2$ TO THE CARBONS IN R[a]

EQUATION NO.	CONDITIONS	EQUATION	DEVIATIONS[b]		
	Pressure, mm.		Members excluded[c]	Maximum	Average
1	4	$T^2\,10^{-4} = 1.09x + 23.1$	1	2	0.7
2	1	$T^2\,10^{-4} = 0.99x + 20.5$	1	1	0.6
3	0.4	$T^2\,10^{-4} = 0.97x + 18.93$	1	1	0.2
	Temp., °C.				
4	200	$\text{Log } p = -0.2465x + 0.477$	1	0.01	0.00
			2	0.00	0.00
5	20	$M/d = 33.75x + 264.4$	1	0.00	0.00
			2[d]	0.00	0.00
6	20	$M/n = 19.15x + 235.5.$	1	0.0003	0.0001

[a] R = n-alkyl group; T = b.p., °K; x = carbon atoms in alkyl group; p = pressure, mm. Hg; $d = d_4^{20}$; and $n = n_D^{20}$.

[b] Given in terms of the physical constant concerned.

[c] First members of the homologous series unless otherwise stated.

[d] Methyl and octyl esters excluded.

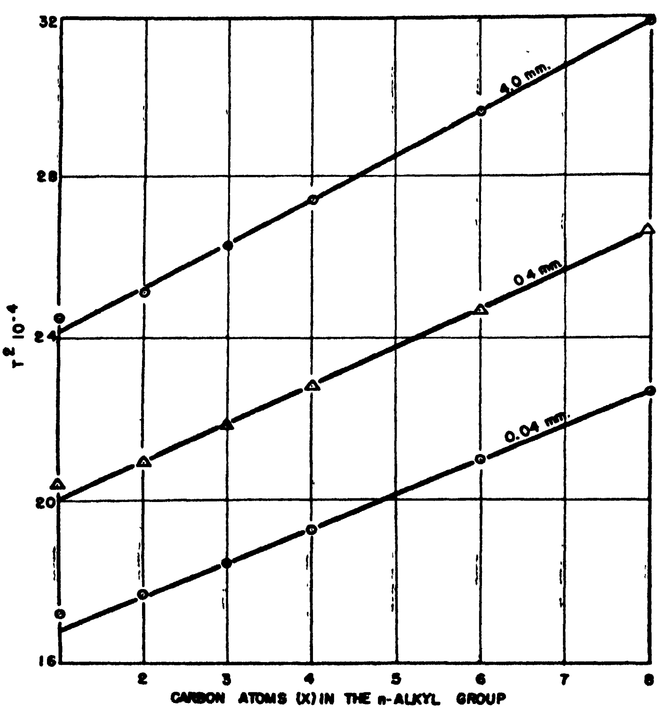

FIGURE 3. Relation between $T^2\,10^{-4}$ and Carbon Atoms (x) of Diethylene Glycol *bis*-Carbonates of n-Alkyl Lactates ($O(CH_2CH_2OCOOCH(CH_3)COO(CH_2)_xH)_2$) (T = b.p., °K.).

the previously recommended method of relating log viscosity to molecular weight was not satisfactory, that is, the relationship was not linear. As usual, the first one or two members of the series did not fit into any of these linear relationships.

The boiling points of the n-alkyl lactate carbonates are a straight line function of the normal boiling points of the corresponding n-alkanols. The relationship is defined by the equation:

$$\text{B.p. of ester at 4 mm.} = 0.534 \text{ (b.p. of ROH at 760 mm.)} + 187$$

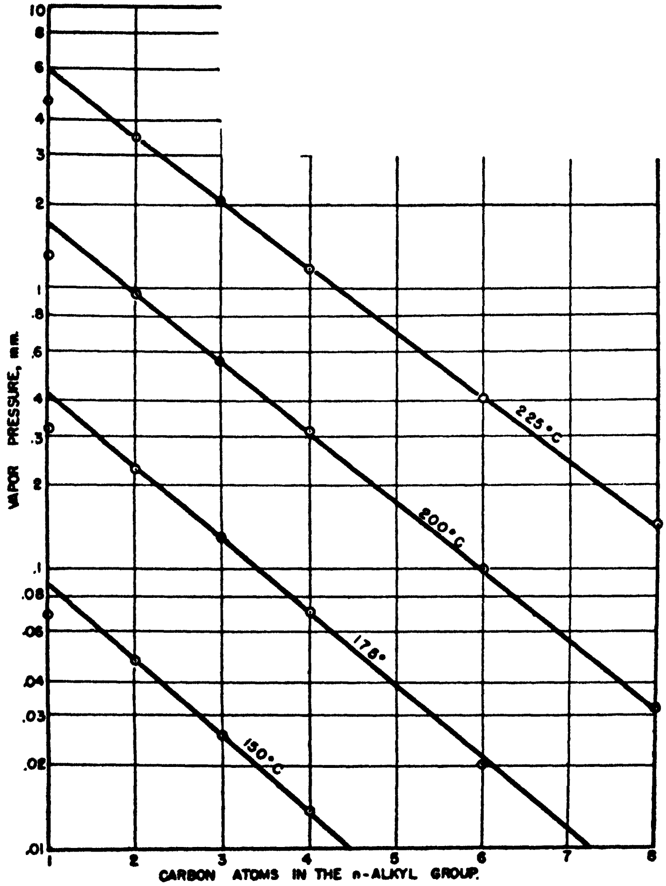

FIGURE 4. Relation Between Vapor Pressures of Diethylene Glycol *bis*-Carbonates of n-Alkyl Lactates and the Number of Carbon Atoms in the n-Alkyl Group.

The boiling points at 4 mm. calculated by this equation for the lactate carbonates prepared from secondary and branched-chain alcohols also are in good agreement with the determined boiling points except for the 2-ethylhexyl ester. The calculated boiling point for this compound is 5.0° high.

The boiling points at 1 mm. of the diethylene glycol bis-carbonates of n-alkyl lactates are compared with those of n-paraffins, n-alkanoic acids, and n-alkyl phthalates in Figure 5. This graphic representation clearly illustrates the un-

usually high boiling points of the lactate carbonates (I) and the relatively low slope of the lines representing the boiling point versus $M^{1/2}$ of polar compounds.

The boiling points of ethers, simple carbonates, and lactate carbonates were compared with each other to ascertain the relative effectiveness of the different functional groups in raising the boiling points (Table IV). The elevating effects are: Carbonate, 60 to 73°; lactate, 33–40°; carbonate plus lactate, 93–106°; and ether, 20°. The effectiveness of the functional groups appears to be inversely proportional to the molecular weight of the lactate carbonate.

Since the boiling points at 3 mm. of n-butyl phthalate (8) and diethylene glycol *bis*-(n-butyl carbonate) (9) are 169° and 175°, respectively, the diethylene

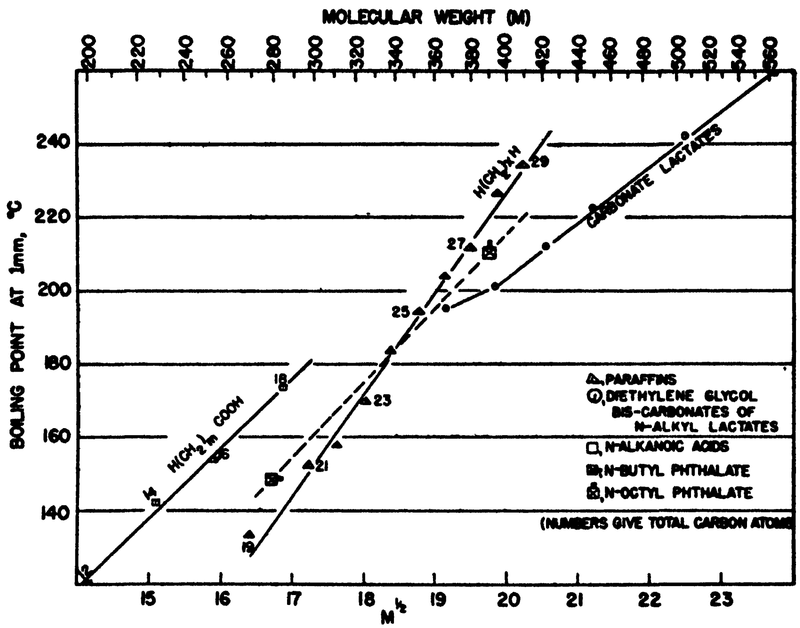

FIGURE 5. Boiling Points at 1 mm. of Diethylene Glycol *bis*-Carbonates of n-Alkyl Lactates, n-Paraffins, n-Alkanoic acids, n-Butyl Phthalate, and n-Octyl Phthalate.

glycol *bis*-carbonates in general might be expected to have boiling points somewhat higher than those of the corresponding phthalates. The boiling points of the lactate phthalates (2) and the alkyl lactate diethylene glycol *bis*-carbonates (I) are in agreement with this generalization. For example, the boiling points at 1 mm. of n-butyl lactate phthalate and n-butyl lactate diethylene glycol *bis*-carbonate (I) are 208° and 221°, respectively.

The diethylene glycol *bis*-carbonates of alkyl lactates (I) prepared from secondary or branched-chain alcohols had higher viscosities than the isomeric n-alkyl compounds. The n-propyl and n-butyl esters had higher densities and refractive indices than the corresponding isomeric esters, whereas the n-hexyl and n-octyl esters had lower densities and refractive indices than the corresponding 2-ethylbutyl and 2-ethylhexyl compounds.

TABLE IV

EFFECTS OF FUNCTIONAL GROUPS ON BOILING POINT[a] OF $O\begin{cases} CH_2CH_2{-}R \\ CH_2CH_2{-}R \end{cases}$

R	B.P., °C. (MM.)	B.P., DIFFERENCES °C[b]	EFFECT OF FUCTIONAL GROUP, °C.	REFERENCE
—OMe	13 (1);			19
	37.6 (5)	183		
—OCOOCH(CH_3)COOMe	196 (1);	189	93[c] (—COOCH(CH_3)COO—)	This paper
	227 (5)			
—Et	20 (4.8)			20
		40	20 (—O—)	20
—OEt	20 (0.4)			
	60 (4.8)			
		163	84[c] (—COOCH(CH_3)COO—)	This paper
		173		
—OCOOCH(CH_3)COOEt	183 (0.4)			
	233 (4.8)	213	106.5 (—OCOOCH(CH_3)COO—)	
—isopropyl	18.6 (1);			
	44.3 (5)	183	93[c] (—OCOOCH(CH_3)COO—)	19
—OCOOCH(CH_3)COO—*i*—Pr	202 (1);	190		This paper
	234 (5)			
—*n*—Bu	46 (3)			
		129	64.5 (—OCOO—)	20
—OCOOBu	175 (3)			
		71	35.5 (—OCH(CH_3)COO—)	9
—OCOOCH(CH_3)COOBu	246 (3)		100 (—OCOOCH(CH_3)COO—)	This paper

[a] Range of values: Ether, 20°; carbonate + lactate, 93–106°; lactate, 33–40°; and carbonate, 60–73°.
[b] Differences between boiling points observed under idential pressures.
[c] Average of two values.

As reported elsewhere (4), some of the diethylene glycol *bis*-carbonates of alkyl lactates, particularly the *n*-butyl, *n*-hexyl, *n*-octyl, and 2-ethylhexyl esters, are good plasticizers for vinyl chloride resins.

Acknowledgment. Analytical data were kindly supplied by C. O. Willits, C. L. Ogg, and their coworkers. The authors are indebted to Franklin Strain of Columbia Chemical Division, Pittsburgh Plate Glass Company, for supplying diethylene glycol *bis*-chloroformate and technical grades of some of the diethylene glycol *bis*-carbonates of alkyl lactates, and to R. L. Bateman of Carbide and Carbon Chemicals Corporation for 2-ethylbutanol and 2-ethylhexanol.

EXPERIMENTAL

Synthesis. Methyl, ethyl, and *n*-butyl lactates are commercially available. The others were prepared by alcoholysis of methyl lactate or by direct esterification of lactic acid (1). They have all been reported in the literature, though *sec-butyl lactate* has not been adequately characterized. The following properties were observed with our material: b.p., 35° (1 mm.); n_D^{20}, 1.4170; d_4^{20}, 0.9734; MR, calc'd, 37.71, obs., 37.76.

The reaction between the lactate and the chloroformate was conducted in ether solution. Pyridine was used to neutralize the hydrogen chloride evolved (1). After the chloroformate had been added to the reaction mixture at about 0°, the mixture was allowed to warm to room temperature. It was then washed to remove pyridine and salts, dried, and distilled.

Physical constants. The distillations and the boiling-point determinations were conducted in an improved tensimeter-still (8), which was continuously agitated by a mechanical shaker. With this equipment, reliable boiling points could be measured at pressures as low as a few hundredths of a millimeter. Pressures in the range 0.01 to 5.0 mm. were measured with a McLeod gauge.

Refractive indices, densities and viscosities were determined with an Abbe type refractometer, Sprengel type pycnometer, and modified Ostwald tube (16, 17), respectively. For these measurements, a constant temperature bath (18) was used to maintain the temperature within ± 0.02°.

Boiling points used in Table IV and in the construction of Fig. 5 were taken from the literature (8, 19, 20).

PHILADELPHIA 18, PA.

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[Contribution from the Department of Chemistry, the University of Texas]

SYNTHESIS OF CERTAIN 5-(2-ALKOXYETHYL)-5-PHENYLHYDANTOINS[1]

HENRY R. HENZE and ROBERT E. LESLIE[2]

Received February 21, 1949

For a long time the only hydantoins reported as possessing an oxy-substituent attached to the 5-position of the heterocyclic nucleus were of either the 5-alkoxy-5-phenylhydantoin or the 5-phenoxy-5-phenylhydantoin types. In 1936 there was reported (1) the synthesis of a few members of the 5-alkoxymethyl-5-alkylhydantoin series and of 5-ethoxymethyl-5-phenylhydantoin. Examples of 5-phenoxymethyl-5-alkyl (or 5-phenyl) hydantoins were next announced (2). The latter resembled the alkoxymethyl derivatives in evidencing activity as anticonvulsants, rather than, as had been anticipated, as hypnotics. In an attempt to increase hypnotic effect in hydantoin derivatives, several 5-[1-(2-chloro-1-chloromethylethyl)-oxy]ethyl-5-alkyl (or 5-phenyl) hydantoins were synthesized (3). This series thus introduced α-substitution into the well-known drug, Nirvanol (5-ethyl-5-phenylhydantoin) (4); however, the 5-phenyl analog proved to be highly toxic[3] due, perhaps, to the halogen content. In a partial attempt to test this conclusion, representatives of the 5-(1-methylpropoxy)ethyl-5-alkylhydantoin series were produced (7). Upon testing one example, it was found to be inactive.

More recently, we have returned to the synthesis of hydantoins containing alkoxyalkyl and alkyl or phenyl substituents (8). Three of these compounds, namely, 5-isopropoxymethyl-5-phenylhydantoin, 5-propoxymethyl-5-phenylhydantoin and 5-ethoxymethyl-5-phenylhydantoin, proved to be the most promising, with respect to efficiency as anticonvulsants, of all hydantoins containing an ether-grouping substituent as yet produced.

Obviously, it was of interest to attempt the synthesis of certain hydantoins isomeric with those enumerated above. It was, therefore, the purpose of the present investigation to prepare 5-(2-methoxyethyl)-5-phenylhydantoin and a few of its homologs.

The first five members of the series of 5-(2-alkoxyethyl)-5-phenylhydantoins have been synthesized by interaction of the corresponding β-alkoxypropiophenones (9) with potassium cyanide and ammonium carbonate. Each of these hydantoins exhibited some degree of activity as anticonvulsants, the 2-methoxyethyl-5-phenylhydantoin being most active. However, all are less active than are the isomeric members of the alkoxymethyl series.

Since acrylophenone was available,[4] an effort was made to convert it into

[1] From the M. A. thesis of R. E. Leslie, June, 1948.

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[3] In almost every case, testing for anticonvulsant activity in these hydantoin derivatives (5, 6) was obtained through the courtesy of Parke, Davis & Co., Detroit, Michigan, to whom our sincere appreciation is expressed.

[4] As a by-product of the preparation of the alkoxypropiophenones, especially from attempted distillation of β-ethoxypropiophenone.

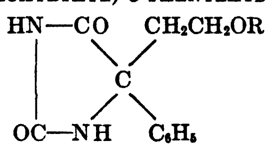
5-phenyl-5-vinylhydantoin. However, the actual product of this attempt proved to be 5-(2-cyanoethyl)-5-phenylhydantoin. This behavior of this vinyl ketone appears to be analogous to that of carvone (10) and of four substituted Δ^2-cyclohexenones (11) in that, under the same conditions of reaction, these unsaturated ketones also were converted into cyano-substituted hydantoins.

EXPERIMENTAL

The *5-(2-alkoxyethyl)-5-phenylhydantoins* were prepared according to the Bucherer method (12) by mixing 1 equivalent of a crude β-alkoxypropiophenone with 1.25 equivalents of potassium cyanide and 4–5 equivalents of ammonium carbonate (U.S.P. cubes) in 6–9 volumes of 70% ethyl alcohol. The mixture was heated in a water-bath at about 60–62° for periods of nine to twelve hours. Filtration from insoluble, inorganic material gave a filtrate which was acidified with concentrated hydrochloric acid. Usually, some solid, organic material precipitated; additional product was obtained by concentration of the filtrate by means of an air jet directed upon its surface.

TABLE I

5-(2-ALKOXYETHYL)-5-PHENYLHYDANTOINS



R	M.P., °C.	YIELD, %	NITROGEN, %		CARBON, %		HYDROGEN, %	
			Calc'd	Found	Calc'd	Found	Calc'd	Found
CH_3	149–150 (dec.)	70	11.96	11.92	61.52	61.11	6.03	6.28
C_2H_5	123–124 (dec.)	29	11.29	11.37	62.88	62.76	6.50	6.70
C_3H_7	140–141 (dec.)	74	10.68	10.72	64.10	64.14	6.92	7.08
$CH(CH_3)_2$	136–137 (dec.)	69	10.68	10.88				
C_4H_9	147.0–147.5 (dec.)	49	10.14	10.22				

The hydantoins were partially purified by solution in 10% sodium hydroxide solution and reprecipitation by addition of solid carbon dioxide. Further purification was achieved by recrystallizations from 50% ethyl alcohol or benzene-Skellysolve mixtures. Data obtained for melting points and from analyses of the hydantoins appear in Table I.

In the case of the *ethoxyethyl member*, the product after recrystallization from diluted alcohol melted at 104–105°. A sample of this material was dried to constant weight in an oven at 75° under 30-inch vacuum and then was found to melt at 123–124° (dec.). Another portion of the material of m.p. 104–105° was dissolved in a large volume of benzene, and the solution was subjected to distillation until the distillate became clear. The residual solution was diluted with anhydrous Skellysolve; material crystallized from solution and had the m.p. 123–124° (dec.). Such material was then recrystallized from 50% ethyl alcohol and, after drying in the air, melted at 104–105°. A weighed sample of the latter was dried in the vacuum oven and suffered a loss in weight of 7.03%; the calculated loss of water for a monohydrated 5-(2-ethoxyethyl)-5-phenylhydantoin is 6.77%.

Anal. Calc'd for $C_{13}H_{16}N_2O_3$: C, 62.88; H, 6.50; N, 11.29.

Found: C, 62.76; H, 6.70; N, 11.37.

Similarly, the recrystallized *isopropoxyethyl analog* melted at 112–114° (out of 50% alcohol), but melted at 136–137° (dec.) after drying to constant weight at 75° in an efficient vacuum oven. Duplicate determinations of the loss of weight of the product melting at

112–114° gave 6.32% and 6.54% (average 6.43%); the calculated loss of water for a monohydrated 5-[2-(1-methylethyl)oxyethyl]-5-phenylhydantoin is 6.43%. In this case also, water of hydration could be removed by partial distillation of a solution of the hydrate in anhydrous benzene; the crystalline product recovered from such treatment with benzene melted at 136–137° (dec.).

Preparation of 5-(2-cyanoethyl)-5-phenylhydantoin. Seven grams of impure acrylophenone,[5] 4.3 g. of potassium cyanide and 16 g. of ammonium carbonate in 70% ethyl alcohol solution was heated at 62° for twelve hours. The reaction mixture was acidified, causing precipitation of the product. The latter was dissolved in dilute sodium hydroxide solution, from which it was reprecipitated upon the addition of solid carbon dioxide. Further purification was difficult and required repeated recrystallizations from diluted alcohol and, finally, fractional recrystallization from water in order to obtain the constant m.p. 186–189°.

Anal. Calc'd for $C_{12}H_{11}N_3O_2$: N, 18.32. Found: N, 18.35.

Preparation of 5-(2-carboxyethyl)-5-phenylhydantoin. Approximately 2 g. of 5-(2-cyanoethyl)-5-phenylhydantoin was refluxed in 30 ml. of 25% hydrochloric acid for two hours. Upon cooling, a precipitate formed and was removed by filtration. It was dissolved in an aqueous solution of sodium bicarbonate and reprecipitated by addition of hydrochloric acid. After drying, the hydantoin derivative melted at 215°.

Anal. Calc'd for $C_{12}H_{12}N_2O_4$: Equiv. wt., 248.2; N, 11.28.
Found: Equiv. wt., 252.5; N, 11.15.

SUMMARY

1. Five examples of 5-(2-alkoxyalkyl)-5-phenylhydantoin, a new type of hydantoin derivative, have been synthesized.

2. Acrylophenone has been converted into 5-(2-cyanoethyl)-5-phenylhydantoin, and the latter subsequently hydrolyzed to 5-(2-carboxyethyl)-5-phenylhydantoin.

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[5] Obtained as the distillate in an attempted distillation of β-ethoxypropiophenone and identified as such by the m.p. of its phenylhydrazone.

[CONTRIBUTION OF THE CHEMISTRY DEPARTMENT COLUMBIA UNIVERSITY]

THE VON BRAUN CYANOGEN BROMIDE REACTION I. APPLICATION TO PYRROLIDINES AND ETHYLENIMINES (1)

ROBERT C. ELDERFIELD AND HOWARD A. HAGEMAN

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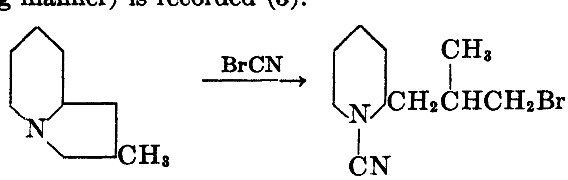
The search for synthetic hypoglycemic agents presents an attractive field for the efforts of the organic chemist. Several synthetic substances have already been explored in this connection, the most noteworthy of which have been Synthalin and Neo-synthalin. However, these two substances are far from satisfactory drugs since their protracted use is accompanied by severe impairment of the glycogenic functions of the liver. Notwithstanding, a further exploration of various synthetic guanidine derivatives presents at present the most hopeful line of approach to the problem of the production of synthetic hypoglycemic agents. In the light of the literature on this subject, further work in the guanidine series demands the synthesis of radically new types of guanidines.

Accordingly, the preparation of various bromoalkylcyanamides as intermediates for the preparation of guanidines appeared to be worthy of study. The classical von Braun ring opening of nitrogen heterocycles under the influence of cyanogen bromide provides a convenient source of such substances. Therefore a systematic study of this reaction has been undertaken, during the course of which several problems presenting distinct chemical interest aside from the major end in view have arisen.

Emphasis has been placed on the manner in which substituted pyrrolidines and ethylenimines undergo ring cleavage with cyanogen bromide to yield the desired cyanamides. No reports of the reaction of cyanogen bromide with any ethylenimine are to be found in the literature. A few examples (2, 3, 4) of the reaction of various pyrrolidines with cyanogen bromide are recorded. Such examples concern the ring opening under the influence of cyanogen bromide of N-alkylpyrrolidines in which no alkyl substituents are carried in the 2- or 5-positions of the pyrrolidine ring. Only one similar ring opening which involves the opening of an indolizidine (in which rupture of the pyrrolidine ring is effected in the following manner) is recorded (3).

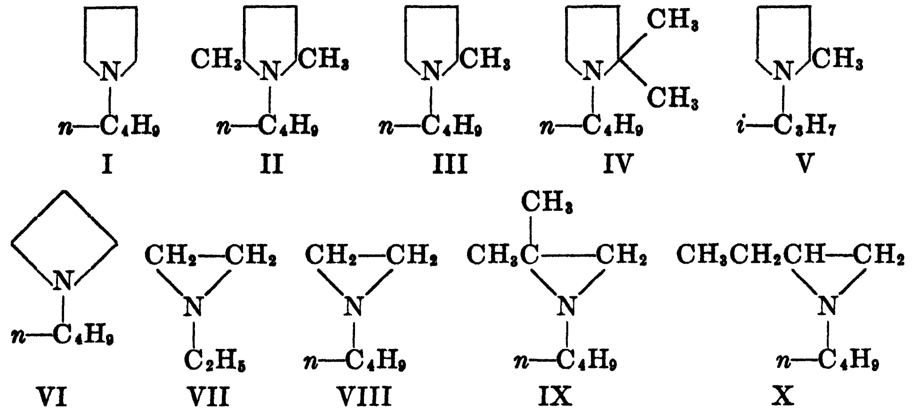


However, in this case, which can be considered analogous to that of an N-alkyl-2-alkylpyrrolidine, rupture of the pyrrolidine ring in the opposite direction would hardly be expected.

Although very extensive studies on the extent of ring opening versus dealkylation under the influence of cyanogen bromide have been made by von Braun,

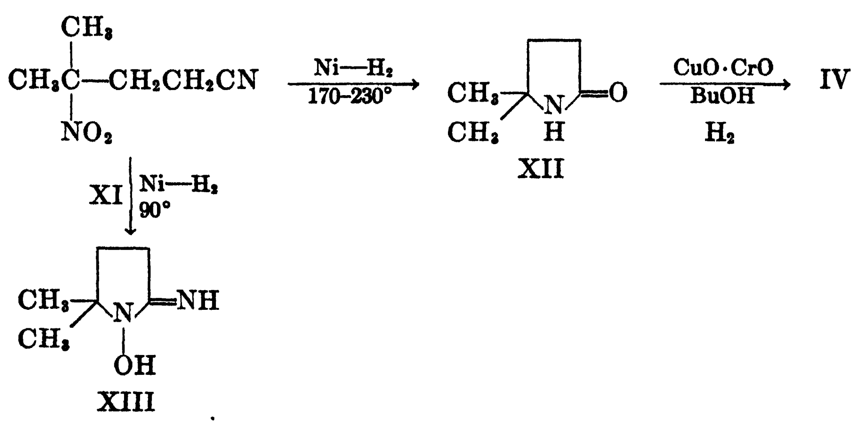
there appear to be no data on the relative amounts of the two possible products resulting from the cleavage of unsymmetrically substituted pyrrolidines.

The following compounds have been prepared in order to study their behavior when subjected to the action of cyanogen bromide:



The preparation of the pyrrolidines, with the exception of IV, afforded no difficulty. The recent availability of 1,4-dichlorobutane and 1,4-dichloropentane (5) opened up an easy route to the pyrrolidines I, III, and V by heating the dihalide with the appropriate amine. This procedure possesses distinct advantages from the point of view of simplicity over that of Coleman, Nichols, and Martens (6) which involves treating an *N*-chlorosecondary amine with sulfuric acid. Pyrrolidine II was readily prepared by catalytic reduction of *n*-butyl-2,5-dimethylpyrrole which was in turn prepared from acetonylacetone and *n*-butylamine.

At the time the present work was begun, no satisfactory method for the preparation of pyrrolidines of the type of IV was available. Lukeš (7) describes what appears to be a rather unsatisfactory preparation of 1,2,2-trimethylpyrrolidine from 1-methyl-2-pyrrolidone and methylmagnesium bromide. A more convenient synthesis for IV has been developed according to formulas XI–XIII.



Yields of XII in the order of 60% were obtained and XII was converted to IV in 45% yield. When XI was reduced under milder conditions a moderate yield of 1-hydroxy-2,2-dimethyl-5-iminopyrrolidine (XIII) was obtained. After this synthesis had been worked out, the excellent study of the reduction of γ-nitronitriles by Buckley and Elliot (8) appeared. Very recently Leonard and Beck (9) have described the preparation of 1,2-diethylpyrrolidine by reduction and hydrogenolysis of ethyl γ-nitrocaproate.

Although Gabriel and Hirsch (10) have prepared ethylenimines by the action of alkali on β-haloamines, the most satisfactory method for the synthesis of these substances is that of Wenker (11) involving treatment of the inner salt of the sulfate ester of a β-aminoalcohol with strong alkali. Since considerable quantities of N-alkylethylenimines were required in the present work a more convenient laboratory procedure which has given consistent yields of N-alkylethylenimines of the order of 70–80% was developed by modification of Wenker's general method. The solid hydrochloride of the amino alcohol is treated with a slight excess of chlorosulfonic acid and the ethylenimine is then steam-distilled from an aqueous alkaline solution of the sulfuric acid ester of the amino alcohol.

When applied to the preparation of N-*n*-butylazetidine, this method gave only a 30% yield. Due to the difficulty of obtaining the requisite azetidines, the present investigation was not extended to this group.

The manner by which tertiary amines react with cyanogen bromide has been well formulated by von Braun (12) as involving formation of an initial intermediate complex:

$$R_3N: + BrCN \rightarrow [R_3NCN]^+ Br^- \rightarrow R_2NCN + RBr$$

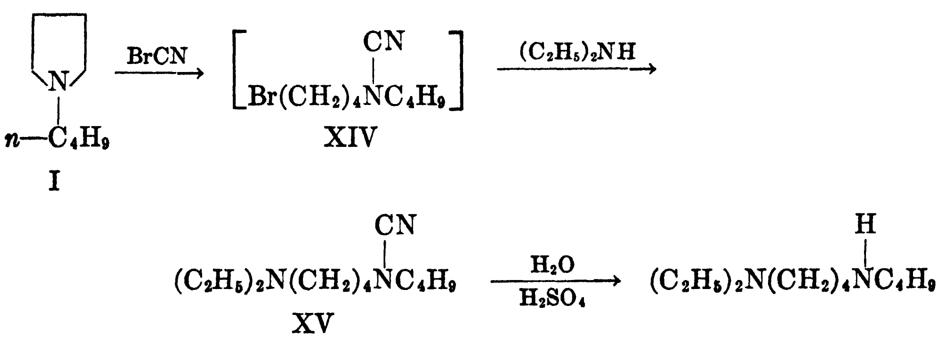
This is in agreement with the mode of cleavage of the cyanogen bromide or chloride molecule to yield a negative bromide or chloride ion under the influence of alkali (13).

In the cleavage of an unsymmetrical tertiary amine the bond broken is determined by the nature of the radicals of the amine. In the more special case of an N-alkyl heterocycle, one mode of cleavage can involve merely elimination of the substituting N-alkyl group without cleavage of the ring. Since von Braun (2) has observed that N-methylpyrrolidine undergoes partial demethylation whereas N-*n*-propylpyrrolidine does not but rather reacts with cyanogen bromide in a manner resulting exclusively in ring cleavage, the experiments here described were carried out with N-*n*-butylpyrrolidines in order to avoid side reactions caused by elimination of the N-substituting group.

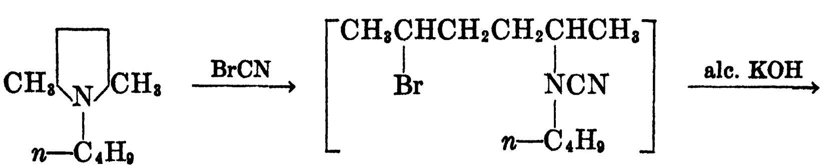
In several cases in which the tertiary amines and cyanogen bromide were mixed all at once with or without a solvent, the formation of considerable amounts of quarternary salt arising from alkylation of the original tertiary amine by the bromide formed on cleavage was noted (14). In order to avoid this side reaction and thus increase the yield of the bromocyanamide all reactions were carried out by slowly adding a solution of the amine to a stirred solution of cyanogen bromide. By taking the above two factors into account the ring open-

ings have been carried out with no detectable formation of quarternary salt and with no detectable debutylation with formation of the N-cyanopyrrolidines. Except in the case of the pyrrolidine IV crude yields of 90–100% of bromoalkylcyanamides resulted from the ring-opening reactions.

Before proceeding to the study of the direction of ring opening of the unsymmetrically substituted heterocycles, development of a method suitable for determining the relative amounts of products formed became necessary. Isolation of the bromocyanamides formed as primary products of the ring cleavage reaction is not suitable since they are somewhat unstable and difficultly separable. For this purpose the action of cyanogen bromide on two symmetrically substituted pyrrolidines I and II was investigated. These substances were chosen because I can lead only to a bromocyanamide containing primary halogen and II to a similar compound containing secondary halogen. The reaction of I with cyanogen bromide has previously been studied by Ochai, Tsuda, and Yokoyama (3) who obtained a 70% yield of *n*-butyl-δ-bromobutylcyanamide (XIV). By the methods now used this yield has been raised to 94% of crude XIV. The crude bromocyanamide (XIV) reacted readily with diethylamine on refluxing for three hours to yield 82% of distillable *n*-butyl-δ-diethylaminobutylcyanamide (XV) which on acid hydrolysis yielded δ-diethylamino-di-*n*-butylamine. Thus a method was provided for demonstrating the structure of similar products.

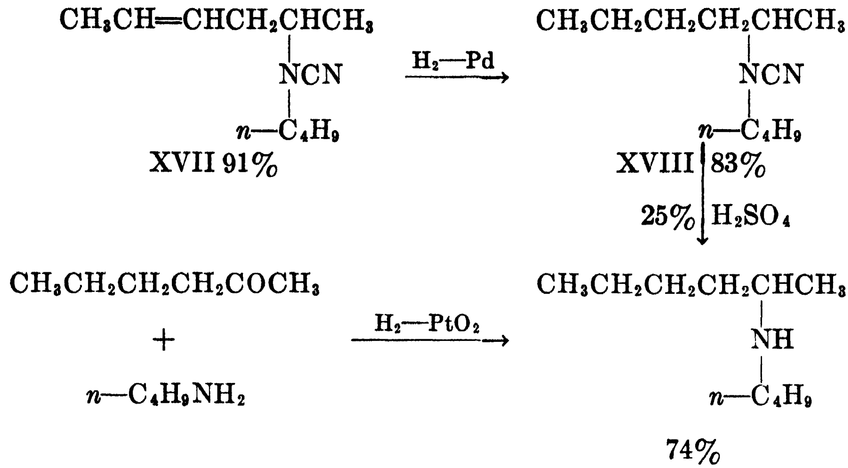


In contrast to the behavior of the bromocyanamide, XIV, on reaction with diethylamine, the secondary bromocyanamide XVI reacted only very sluggishly if at all, 96.4% of unreacted XVI being recovered. Therefore, in order to characterize the bromocyanamide (XVI) and to demonstrate its structure it was dehydrobrominated to XVII



II

XVI 94%



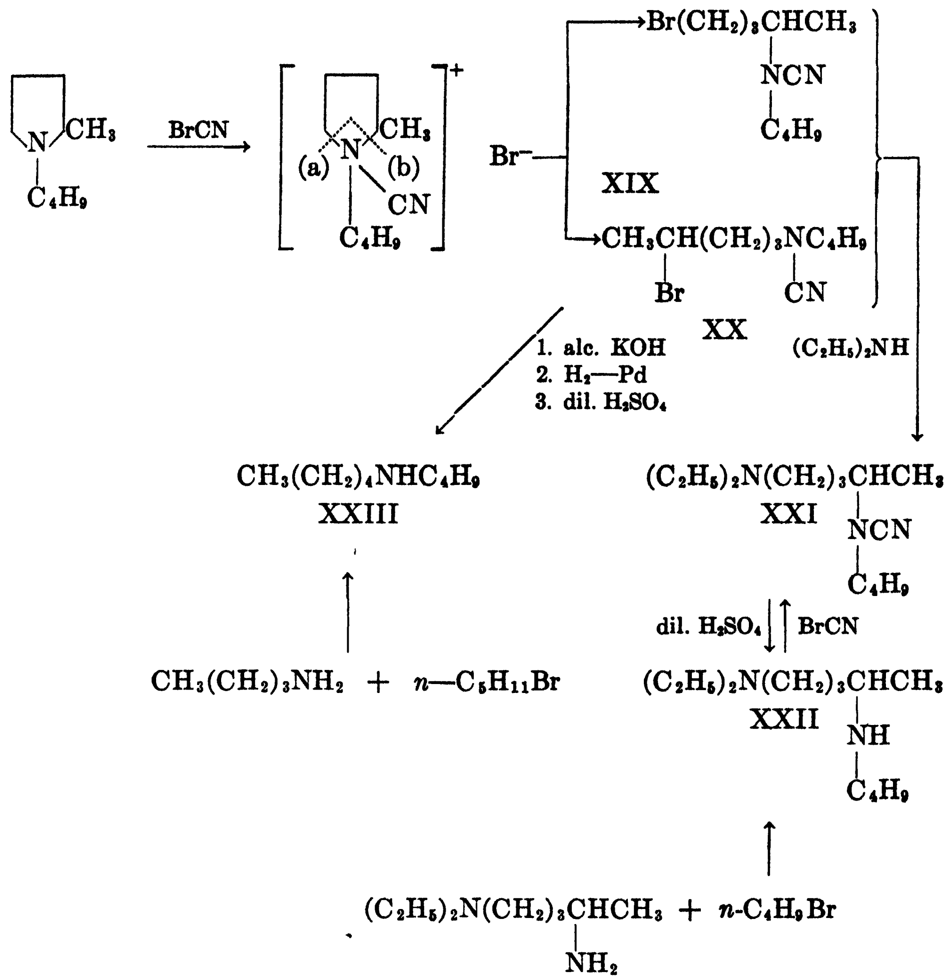
in which the position given the double bond is purely arbitrary. Hydrogenation of XVII to XVIII followed by hydrolysis of the latter gave 2-*n*-butylaminohexane which was also prepared by reductive amination of hexanone-2 with *n*-butylamine.

Finally, in order to establish the usefulness of the reaction with diethylamine as a means of differentiating bromocyanamides containing a primary halide from those containing a secondary halide, mixtures of XIV and XVI were subjected to the action of diethylamine under conditions identical to those used with the individual substances. Crude non-basic XVI was recovered to the extent of 95% of the XVI taken, and crude basic XV was found to the extent of 99% of the XIV taken. This difference in the observed reactivity of the two halides under these conditions is in accord with the observation of Morell (15) who reports substantially complete separation of 1-bromo-4-acetoxypentane from 1-acetoxy-4-bromopentane by treatment with diethylamine. The primary bromide reacts readily, while the secondary bromide reacts in negligible amounts. Data reported by Hass and Huffman (16) and by Conant and Hussey (17) also indicate a considerable difference in reactivity between primary and secondary halides in similar reactions.

When a substance such as 1-*n*-butyl-2-methylpyrrolidine (III) undergoes ring opening with cyanogen bromide, two isomeric bromoalkylcyanamides (XIX and XX) are possible products. If the mechanism of the cleavage involves a nucleophilic displacement by bromide ion, then a higher proportion of cleavage at (a) than at (b) would be expected in accordance with the generally observed faster rate of displacement reactions involving primary alkyl linkages as compared to secondary linkages. On this basis XIX should be the major component of the product of the ring cleavage.

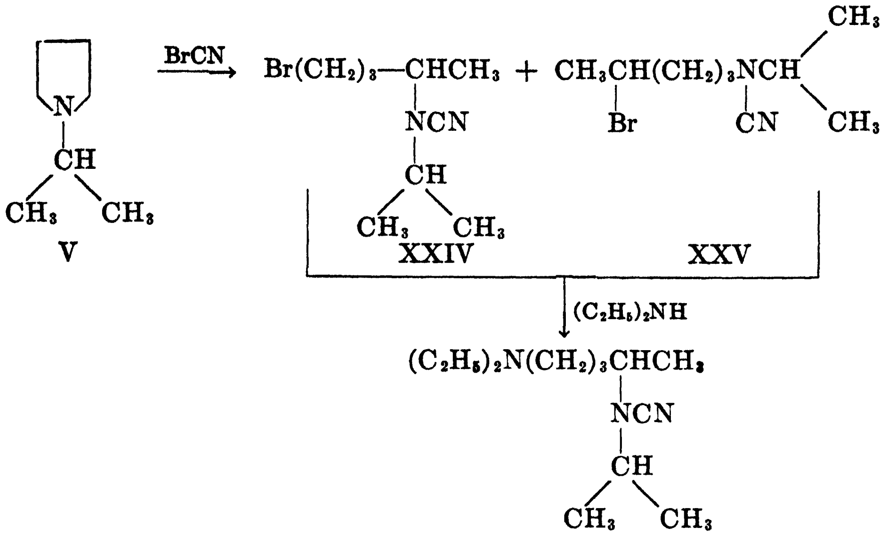
When a solution of 1-*n*-butyl-2-methyl pyrrolidine (III) in benzene was added slowly to a benzene solution of cyanogen bromide, a 98% yield of a crude mixture of isomeric bromoalkylcyanamides was obtained. Separation and identifica-

tion of the isomers comprising this mixture were effected according to the following scheme:



From two separate experiments identical crude yields of 70% of isomer XIX and 26% of isomer XX were obtained. The diethylaminocyanamide (XXI) prepared as indicated by the two methods was characterized as the oxalate and was hydrolyzed in 86% yield to the diamine (XXII). The hydrochloride of XXII was identical with the same substance prepared by butylation of 1-diethylamino-4-aminopentane. The bromocyanamide (XX) was converted by three steps to *n*-amyl-*n*-butylamine (XXIII) in 48% yield. The picrolonate of the amine thus obtained was identical with that resulting from amylation of *n*-butylamine.

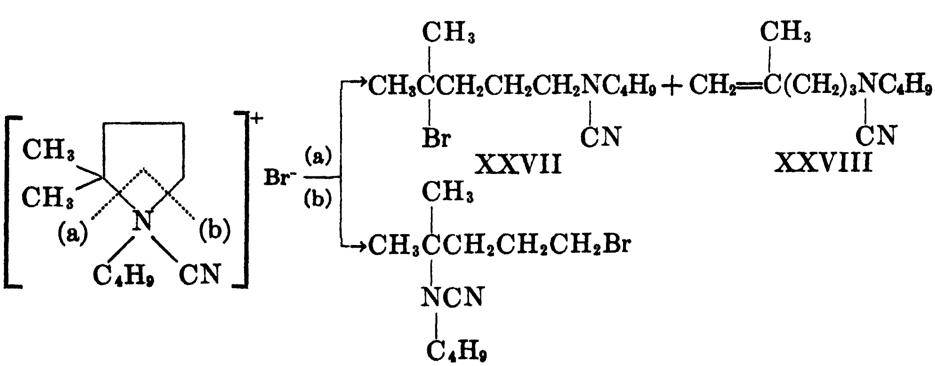
In order to determine the effect of a secondary alkyl substituent on the nitrogen of the pyrrolidine, cleavage of 1-isopropyl-2-methylpyrrolidine (V) was investigated.



V; XXIV; XXV; XXVI

A crude yield of 94% of mixed cyanamides, XXIV and XXV, was obtained. Separation of the mixture as in the previous case showed it to consist of 32% of XXV and 65% of XXIV, the latter figure being calculated on the basis of crude XXVI isolated. Although XXVI was characterized as the oxalate, no work was done to establish definitely the structures of XXIV and XXV. The argument here rests solely on analogy with the preceding case.

When considering the products of the ring opening of a substance such as 1-*n*-butyl-2,2-dimethylpyrrolidine (IV) with cyanogen bromide, the possible formation of three products must be taken into account:

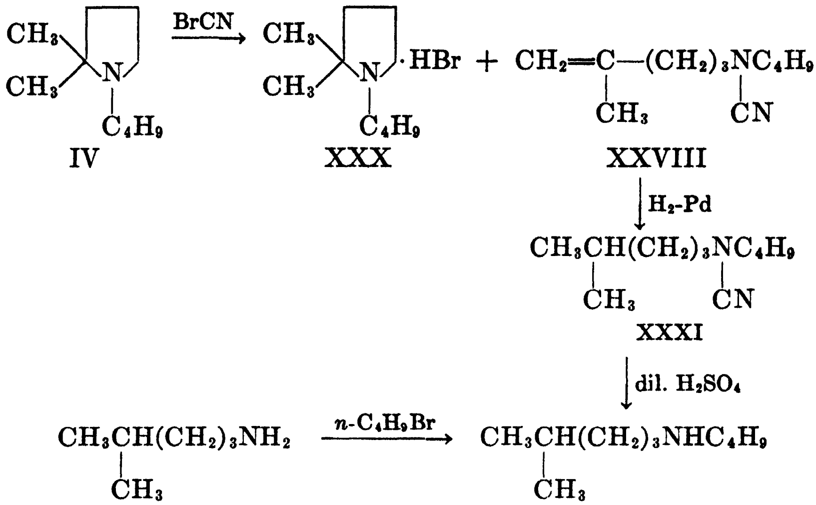


XXVII; XXVIII; XXIX

In a non-polar solvent such as benzene or ether, cleavage at (a) by means of a solvolytic reaction would not be expected and the formation of XXVII would seem unlikely. A more logical type of cleavage at (a) would involve an elimination reaction resulting in the formation of XXVIII. A second order nucleophilic

displacement reaction appears to account most reasonably for cleavage at (b) with the formation of XXIX.

When cleavage of the pyrrolidine (IV) was carried out in ether or benzene substantially the same products were obtained in essentially the same yields in both cases. The mode of cleavage of IV and the identification of the products is shown in the following formulas:



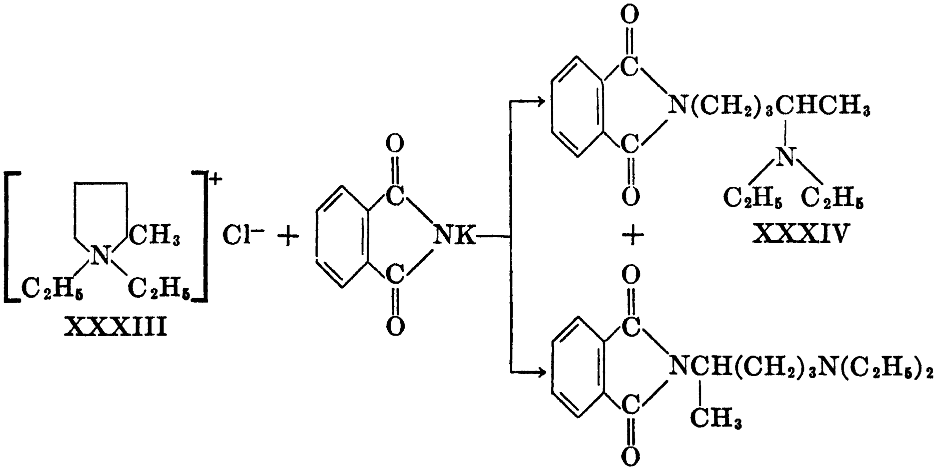
IV XXX XXVIII XXXI XXXII

When the reaction was carried out in anhydrous ether, a white solid (XXX) separated. This was characterized as the hydrobromide of the pyrrolidine IV. The only acid-insoluble, non-basic product isolated from the reaction mixture was XXVIII in which, as previously, the position of the double bond is assigned arbitrarily. In a typical experiment starting with 0.320 mole of IV, total recovery of IV both as such and as its hydrobromide (XXX) was 0.136 mole. Crude XXVIII was isolated in the amount of 0.135 mole which is consistent with the amount of IV recovered and excludes the formation of significant amounts of other possible products. The quantity of hydrogen bromide (0.136 mole) required for the formation of XXX could result from the formation of an equimolar amount of XXVIII.

Apparently the hydrobromide (XXX) is appreciably more soluble in benzene than in ether since the above reaction when carried out in benzene resulted in no precipitation of XXX. In this case all of the recovered starting material was isolated as the free base (IV). To determine if any XXIX had been formed, the neutral fraction from the reaction mixture was refluxed with excess diethylamine. From this 85% of non basic material was recovered and only 1.0 per cent of oily basic material was found. On the basis of this experiment, it may be concluded that ring opening proceeded to yield exclusively the unsaturated cyanamide (XXVIII).

Closely related to the problem at hand is the work reported by Kharasch and Fuchs (18) in which the reaction of pyrrolidinium halides with potassium phthali-

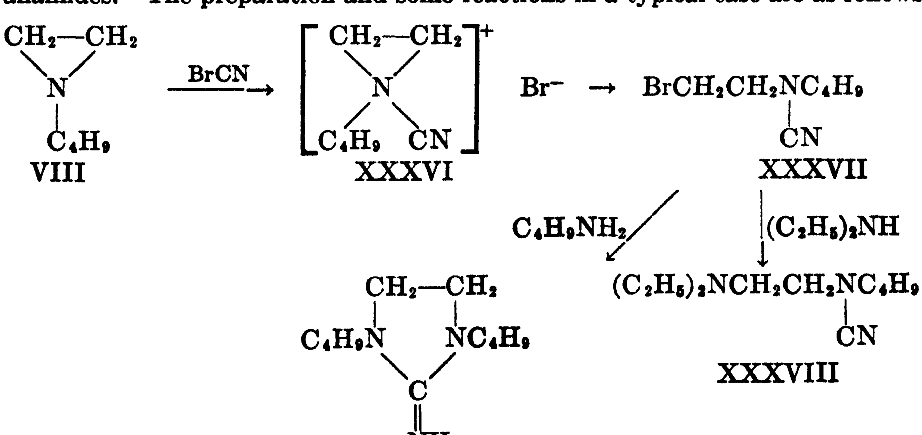
mide at 150–160° is described. Rupture of the pyrrolidine ring in XXXIII as represented by the following equations is reported:



XXXIII XXXIV XXXV

Yields of crude mixtures of XXXIV and XXXV resulting from the ring opening of 80–85% are given. Fractionation through a 100-plate column of the products of the hydrolysis of the mixture of XXXIV and XXXV indicated that the mixture consisted of 90% of XXXIV and 10% of XXXV.

Ring cleavage of N-substituted ethylenimines by cyanogen bromide is unique in that it affords ring-opened products of far greater stability than the haloamines resulting from cleavage with hydrogen halides. When the reaction is properly carried out by the gradual addition of an ether solution of the imine to a stirred ether solution of cyanogen bromide, good yields of β-bromoethylcyanamides can be obtained from simple N-substituted ethylenimines. Thus N-n-butylethylenimine and N-ethylethylenimine give 94% and 88% respectively of the bromocyanamides. The preparation and some reactions in a typical case are as follows:



VIII XXXVI XXXVII XXXVIII XXXIX

In contrast to epoxy compounds, ethylenimines, in the absence of electrophilic reagents, are very stable toward ring opening. However when the nitrogen is converted to the quaternary state the ring is ruptured with extreme ease, *e.g.*, the ready formation of β-haloamines by treatment of ethylenimines with hydrogen halides (19, 20). The behavior of ethylenimines with cyanogen bromide parallels the reaction with halogen acids in so far as the easy rupture of the ring in the postulated quaternary intermediate is concerned.

The β-bromoalkylcyanamides are relatively stable and can be purified by vacuum distillation, although a freshly distilled sample gradually darkens after a few days at room temperature. They are unaffected by transient treatment with aqueous alkali or acid. This greater stability as compared to the haloamines can be attributed to the greatly lowered basicity of the nitrogen atom due to the presence of the cyano group. The fact that these cyanamides are insoluble in 25% sulfuric acid confirms the lack of any significant nucleophilic character in the cyanamide grouping. Therefore one would not expect step XXXVI–XXXVII to be reversible.

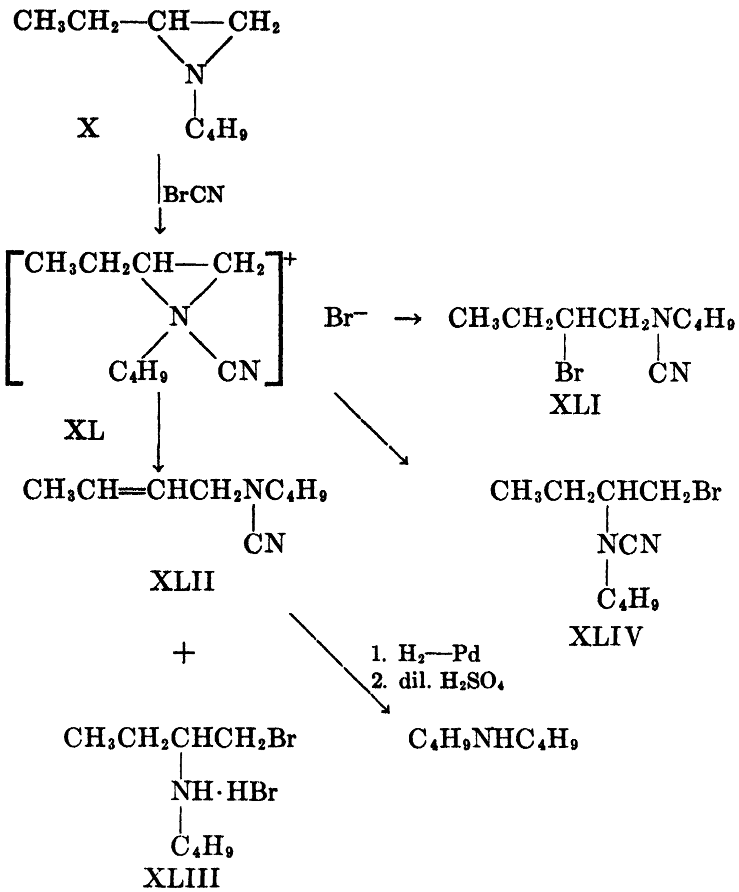
It has been established that when β-haloalkylamines act as alkylating agents, they may first undergo cyclization to an ethylenimmonium ion which is the actual alkylating agent (21). An analogous situation when the bromocyanamides are used as alkylating agents as in the formation of XXXVIII and XXXIX does not seem likely because of the properties of the cyanamides discussed above. Rather, a normal displacement of the bromine by the reagent involved would appear to be the process involved.

Reaction of the bromoalkylcyanamide (XXXVII) with a secondary amine proceeds at a moderate rate without use of a diluent. On the other hand the reaction with a primary amine proceeds with almost explosive violence. By use of a diluent, such as alcohol, cyclic guanidines of the type of XXXIX can be prepared smoothly and in good yield. The mechanism of the formation of these guanidines can be considered similar to that by which ethyleneguanidine results from the action of cyanogen bromide on ethylenediamine (22).

As representative of an N-substituted ethylenimine also carrying a single substituent on one of the carbon atoms, the action of cyanogen bromide on 1-*n*-butyl-2-ethylethylenimine (X) was investigated. The expected cleavage products may be formulated as in XL–XLIV.

When an ether solution of X was added very slowly to an ether solution of cyanogen bromide, a small amount of a white precipitate separated. This was identical with the hydrobromide of the bromoamine obtained by the action of hydrogen bromide on the ether solution of the ethylenimine X. Although the structure of this bromoamine has not been definitely settled, it is assigned the structure XLIII on the basis of the following earlier observations. Gabriel and Ohle (23) and Smith and Platon (24) have shown that propylenimine opens with hydrogen halides to yield the primary alkyl halide. Gensler (25) also reports the cleavage of 1-sulfonyl-2-bromomethylethylenimine to give the primary halide.

The non-basic water-insoluble material resulting from the reaction, on vacuum

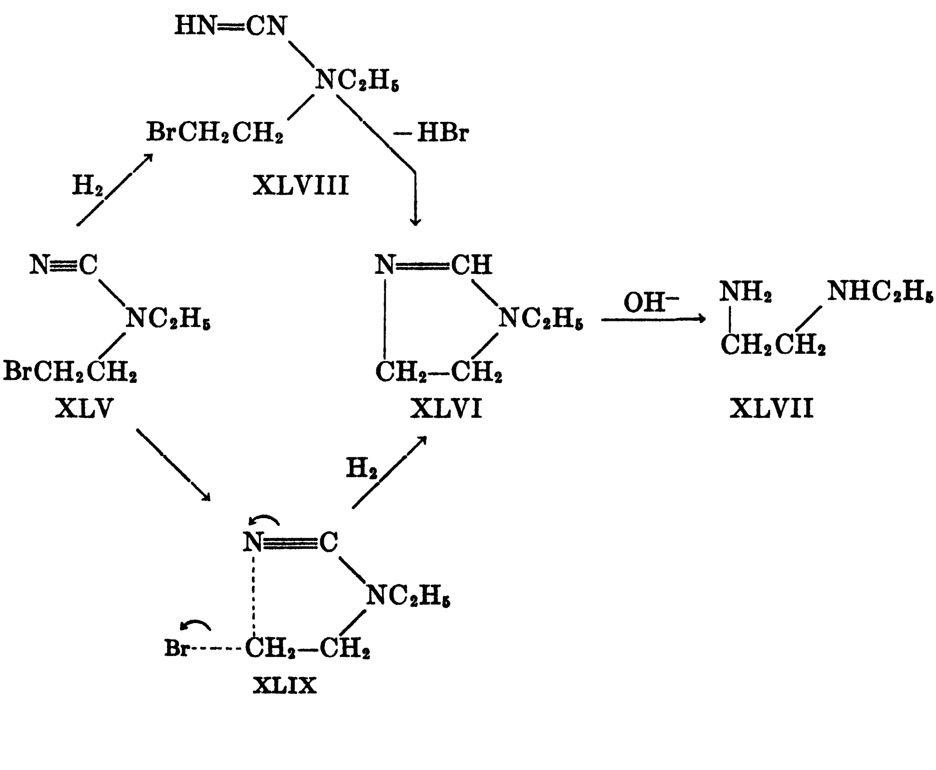


distillation yielded a small forerun which was shown to consist mostly of the cyanamide XLII by its conversion to di-*n*-butylamine. The position of the double bond in XLII is assigned on arbitrary grounds. The main product, amounting to some 53% of distilled material furnished satisfactory analytical figures for either of the bromoalkylcyanamides XLI or XLIV or a mixture of the two. The problem of determining the relative amounts of the two substances in this product was not settled in such a clean-cut manner as with the bromoalkylcyanamides arising from the opening of the pyrrolidines.

When the mixture of XLI and XLIV was treated with diethylamine, 90% of the material taken was recovered as a neutral fraction, which after purification, gave analytical figures for the bromoalkylcyanamide. However it cannot be concluded that the mixture consists predominantly of XLI. Such a conclusion would be based on the assumption that typical primary and secondary bromines occur in XLI and XLIV. The influence of the neighboring cyanamido and ethyl groups in the β-position to the bromine on the reactivity of the bromine in compounds of this type is not known and may be such as to lower the reactivity of the bromine considerably. The deactivating influence of such a β-cyanamido

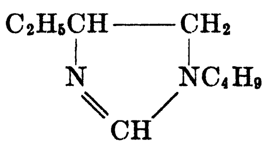
group appears to be relatively unimportant since when *n*-butyl-β-bromoethylcyanamide (XXXVII) was similarly treated with diethylamine a 71% yield of the diethylaminocyanamide (XXXVIII) resulted. Any significant effect of the cyanamido group should make itself apparent in both XXXVII and XLI. This evidence indicates that the major product of the reaction of the ethylenimine (X) with cyanogen bromide may be XLI. This interpretation is supported by the recovery of 80% of neutral starting material when the mixture under consideration was refluxed with benzylamine in alcohol in an attempt to prepare a cyclic guanidine of the type of XXXIX. Under similar conditions XXXIX is readily formed from the β-bromoethylcyanamide (XXXVII) on treatment with *n*-butylamine.

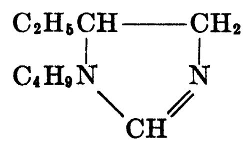
When catalytic removal of the bromine in the mixture of XLI and XLIV by reduction over Raney nickel was attempted, the reaction took an interesting and unexpected course. In methanol solution with a large amount of catalyst, one equivalent of hydrogen as required for removal of the bromine was taken up. However instead of the expected neutral cyanamide derivative, the product isolated from the reduction was a strongly basic substance sparingly soluble in water. Therefore, the similar reduction of the more available ethyl-β-bromoethylcyanamide (XLV) was investigated. Reduction was very rapid in this case and the product isolated after warming with alkali was identified as N-ethylethylenediamine (XLVII). Although the proposed intermediate, XLVI, was not isolated, the course of the reaction can be explained on the assumption of its formation as the initial product of the reduction of XLV by the following steps: (A) re-



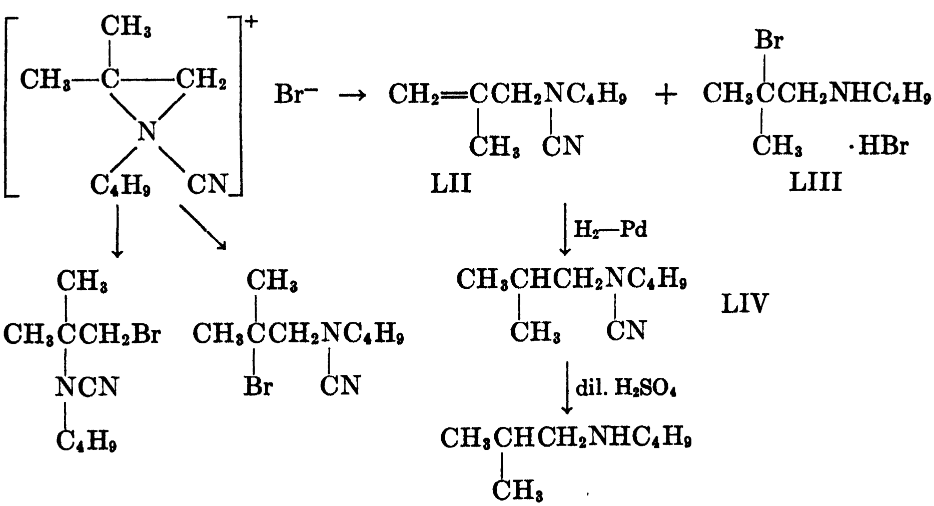
moval of the bromine from XLV via a transition state such as XLIX with reduction to the cyclic amidine (XLVI), (B) hydrolysis of XLVI to yield the diamine XLVII). The alternate route to XLVI via XLVIII does not appear likely since it involves reduction of the cyano group. It has been consistently observed throughout this work that cyanamides are not readily attacked under these conditions by catalytically activated hydrogen. The reaction XLV to XLVI is very rapid and is over in about five minutes.

The product from the reduction of the mixture of XLI and XLIV was isolated as the free base by treatment with alkali in the cold. Due to its extremely hygroscopic nature not entirely satisfactory analytical figures could be obtained. No satisfactory salt could be found. The neutralization equivalent was consistent with either structure L or LI. While no further work has been done at present on these substances, their formulation as imidazolines is consistent with the mechanism for the reduction discussed above. Further investigation of this point will be undertaken.


L


LI

The reaction of 1-*n*-butyl-2,2-dimethylethylenimine with cyanogen bromide was not as clean cut as the ring openings discussed above. By postulating the same general type of intermediate complex, the possible modes of ring cleavage may be represented as follows:

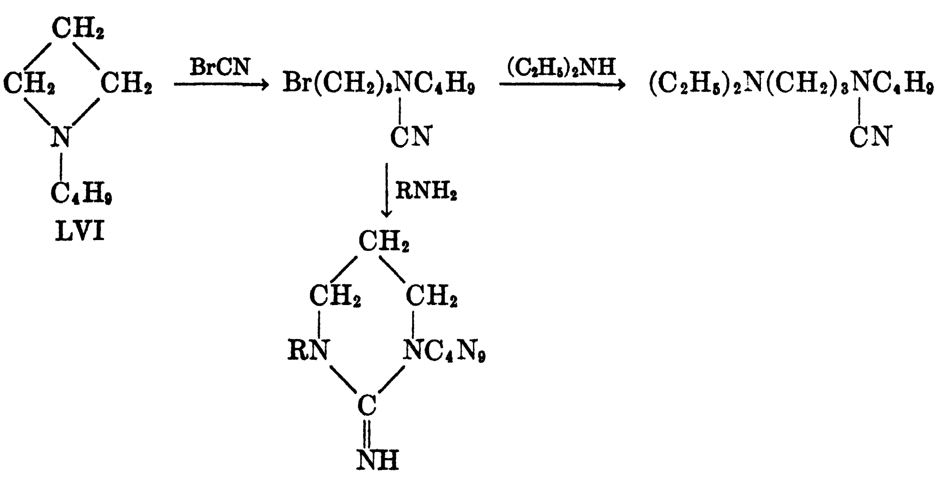

LV

When the reaction was carried out by the very gradual addition of an ether solution of the imine to a stirred ether solution of cyanogen bromide, precipitation of

a white solid began shortly. This behavior is similar to that observed in the cleavage of 1-*n*-butyl-2,2-dimethylpyrrolidine which proceeds exclusively by an elimination reaction at the tertiary alkyl linkage. From 0.62 mole of the imine 0.10 mole of the solid amine hydrobromide (LIII) was isolated. This was identical with the bromoamine hydrobromide obtained by cleavage of 1-*n*-butyl-2,2-dimethylethylenimine with hydrogen bromide, and while its structure has not been proved unequivocally, the structure LIII appears to be most likely by analogy with other published work. Cairns (11) reports the cleavage of 2,2-dimethylethylenimine with dilute sulfuric acid as yielding amino-*tert*-butanol. Campbell and Campbell (26) likewise state that 2,2-dimethylethylenimine opens with hydrogen chloride to give the tertiary chloride.

From the ether-soluble neutral material obtained in the reaction, 0.18 mole of the unsaturated cyanamide (LII) was obtained. The structure of this, exclusive of the position of the double bond, was shown by conversion to *n*-butylisobutylamine (LV) as shown. The amount of LII isolated corresponded to about 30% of the crude ether-soluble neutral material and the total amount of LII and LIII isolated accounted for about 45% of the starting ethylenimine. The remainder of the ether-soluble material was a red-brown gum, possibly polymerized ethylenimine, from which no chemical individual was isolated. While no bromocyanamides were isolated, this does not preclude the possibility of their formation.

The reactions of N-*n*-butylazetidine (LVI) are similar to those of the corresponding ethylenimine:



LVI

LVII

The only difference lies in the formation of a six-membered cyclic guanidine (LVII). Although all of these reactions proceed in good yield thus opening up a wide variety of guanidines, the limiting factor in their usefulness is the lack of a suitable method for the synthesis of azetidines in good yield.

Though a sufficiently large number of cases has not yet been studied to justify

any broad generalizations, the data presently at hand have led to some conclusions worth summarizing.

A pyrrolidine of the type of 1-*n*-butyl-2,5-dimethylpyrrolidine (II) undergoes ring opening with cyanogen bromide to yield a secondary alkyl bromide with no detectable amount of olefin formation and gives a yield of bromoalkylcyanamide comparable to that obtained from the ring opening of a pyrrolidine carrying no substituents in the α-positions.

An unsymmetrically substituted pyrrolidine such as 1-*n*-butyl-2-methylpyrrolidine (III) has been shown to undergo ring cleavage in both directions, yielding predominantly the primary alkyl bromide.

When competition between the cleavage of a nitrogen-primary alkyl linkage and a nitrogen-tertiary alkyl linkage is possible, the reaction proceeds essentially with rupture of the latter linkage with the formation of an olefin as exemplified by the ring opening of 1-*n*-butyl-2,2-dimethylpyrrolidine (IV).

Simple N-alkyl ethylenimines, bearing no alkyl substituents on either carbon atom, have been cleaved in excellent yields with cyanogen bromide to afford the new and chemically interesting β-bromoethylalkylcyanamides.

An ethylenimine such as 1-*n*-butyl-2-ethylethylenimine (X) which can cleave at either the primary alkyl-nitrogen linkage or the secondary alkyl-nitrogen linkage has been shown to cleave to a small extent at the latter linkage with olefin formation and to give as the main product, in moderate yield, a bromoalkylcyanamide. Sufficient work has not yet been done to conclude whether this product is predominantly a primary or secondary alkyl bromide.

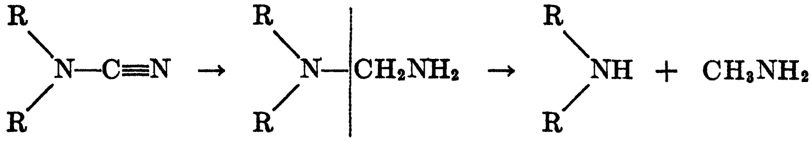
As in the pyrrolidine series, an ethylenimine such as 1-*n*-butyl-2,2-dimethylethylenimine (IX) which can cleave at either a primary or a tertiary alkylnitrogen linkage does so predominantly at the latter linkage with olefin formation. As yet, there has been isolated no bromoalkylcyanamide from this cleavage.

A simple N-alkyl azetidine has been shown to cleave to give in good yield a γ-bromopropylalkylcyanamide.

When various unsaturated cyanamides were subjected to catalytic hydrogenation, there was observed the formation of moderate amounts of basic reduction products which presumably resulted from a partial hydrogenation of the cyanamide group. This behavior has also been observed by Ochiai and Tsuda (4) and by Winterfeld and Holschneider (27) during the catalytic removal of bromine from bromoalkylcyanamides. As a basic side product, Winterfeld and Holschneider report the isolation of a compound in which they consider the basic group to be $>NCH_2NH_2$ on the basis of an analysis of the chloroplatinate.

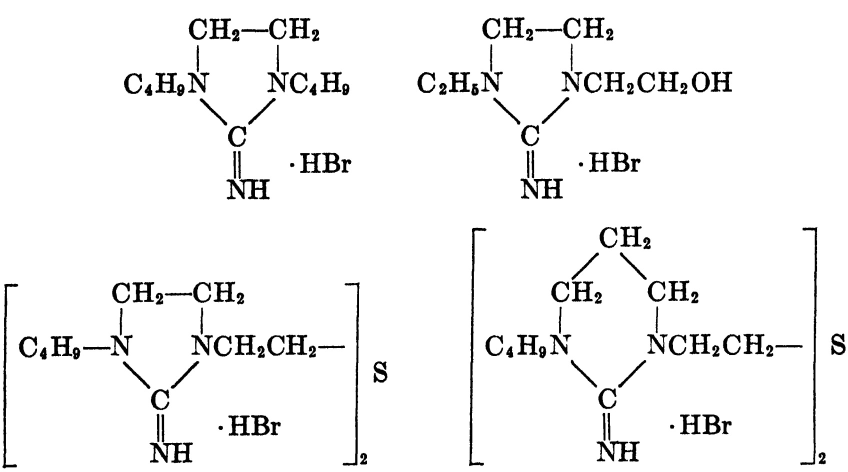
In order to find out how readily and in what manner the cyanamide grouping would undergo catalytic reduction, a sample of *n*-butyl-δ-diethylaminobutylcyanamide (XV) was submitted to catalytic hydrogenation. As shown in the experimental section, this reduction does not proceed very readily. Since the reduction of the dialkylcyanamide group yielded the secondary amine, N-*n*-butyl-

N′-diethylputrescine, the following seems to represent a reasonable course for this reduction:



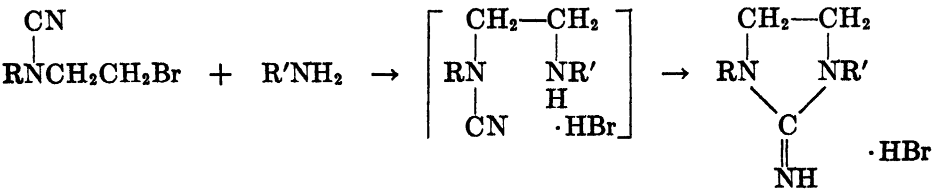
This type of catalytic removal of the cyano group may be of value in cases where a compound is sensitive to strongly acid or alkaline hydrolysis.

Although the different bromoalkylcyanamides prepared in this work can be employed for the synthesis of a great variety of guanidines, only a few of a rather unique type have been prepared. The simplicity of the preparation of cyclic guanidines from either a β-bromoethyl- or a γ-bromopropyl-cyanamide and a primary amine opens up a method for the future preparation of a wide variety of such compounds. The following have been prepared for orientation in testing as potential hypoglycemic agents:



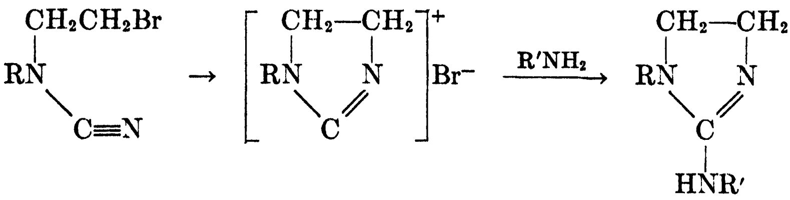
As mentioned previously, compounds of this type result from a rather vigorous reaction between the bromocyanamide and one equivalent of a primary amine.

The general Erlenmeyer method of preparing guanidines from a cyanamide and the salt of an amine apparently represents an intermediate step in this reaction which can be given for the general case as follows:



LVIII

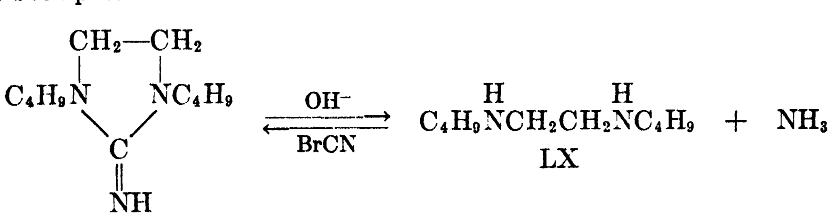
However, in view of the previously noted anomalous behavior of these β-bromoethylcyanamides upon catalytic reduction in which the nitrogen atom of the nitrile group has apparently displaced the bromine atom, a possible alternate mechanism for this reaction can be considered. Such a reaction course would lead to compounds of the type of LVIII, which would be isomeric with those of the type of LIX. One observation which



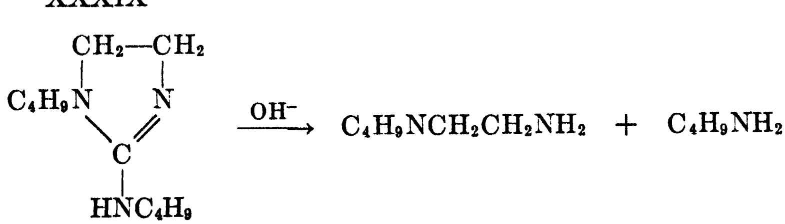
LIX

seems to favor the first mechanism in which the bromine is displaced directly by the amine was the vast difference in the vigor of reaction of the bromocyanamide with a primary amine versus a secondary amine. If the second mechanism were in operation, the reaction with both a primary and a secondary amine should yield guanidines in much the same manner.

For one case, that of XXXIX, the structure has been proved to be as indicated rather than the possible isomeric structure of the type of LXI and the remainder of the guanidines are assumed to have similar structures. The method of this simple proof can be readily understood from the following equations which consider both possible structures.



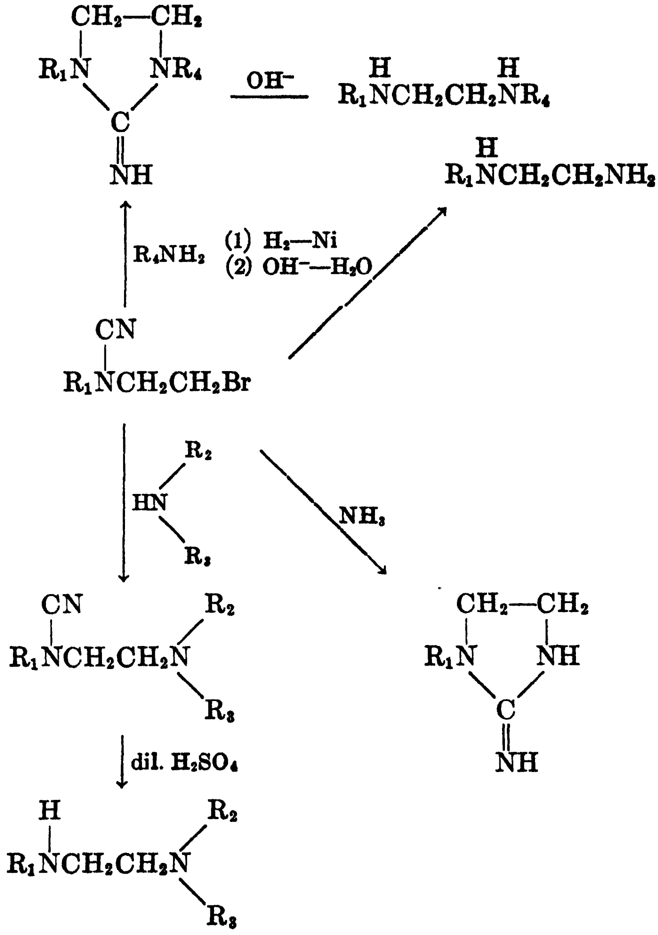
XXXIX



LXI

Hydrolysis of a sample of the guanidine with aqueous alkali yielded a compound (LX) which, on treatment with cyanogen bromide, reformed the original guanidine hydrobromide. By considering the above equations, it is readily seen that the only one of the two possible structures consistent with these results in XXXIX.

As a result of the various reactions of β-bromoethylcyanamides noted in this work, one example of the potential synthetic value of these compounds may be brought out by considering their applicability to the preparation of various alkylated ethylenediamines otherwise difficultly obtainable.



Here the nature of the groups R_1, R_2, R_3, and R_4 can be varied practically at will and the products should be obtained in a relatively pure state.

EXPERIMENTAL (28, 29)

I. PREPARATION OF THE NITROGEN HETEROCYCLIC COMPOUNDS.

A. ETHYLENIMINES

N-(n-Butyl)-ethylenimine (VIII). The slightly hygroscopic hydrochloride of N-(*n*-butyl)ethanolamine (b.p. 102–103°/20 mm.) (30) was prepared by treating an absolute ether solution of the amino alcohol with dry hydrogen chloride. To 117 g. of the crude hydrochloride was added cautiously, under a good hood, 145 g. of freshly distilled chlorosulfonic acid in portions with shaking. After the initial vigorous reaction had subsided, the mixture, protected with a calcium chloride tube, was heated on the steam-bath for forty min-

utes and then heated in an oil-bath first at 80° under water pump vacuum and finally at 140–145° for one and one-half hours. The light-brown gummy residue, after cooling, was dissolved by long stirring in 200 ml. of cold water. This solution was added to a solution of 280 g. of potassium hydroxide in 300 ml. of water contained in a 2-liter 3-necked flask in portions with vigorous agitation. The flask was intermittently cooled under the water tap during the addition so that the temperature of the mixture did not exceed 60–70°. After adding 2 ml. of propylene glycol to reduce frothing, the mixture was steam-distilled, a few pellets of potassium hydroxide being placed in the receiver. A total of about 500 ml. of distillate was collected. After addition of 60 g. of potassium hydroxide, with cooling, the distillate was extracted with three 150-ml. portions of ether. After drying the combined extracts with potassium carbonate there was obtained 55 g. (74%) of material boiling at 104–108°. Redistillation over sodium gave 51 g., b.p. 106–108°; n_D^{25} 1.4118.

Anal. Calc'd for $C_6H_{13}N$: C, 72.6; H, 13.2; N, 14.1.
Found: C, 72.6; H, 13.6; N, 14.3.

N-Ethylethylenimine (VII). This substance has been prepared previously in low yield by Lasselle and Sundet (19). It can be prepared by substantially the method described above in about 70% yield. Difficulty was encountered in separating the imine from the ether used to extract it from the steam-distillate. Therefore, the distilled ether solution was used directly for the subsequent ring opening with cyanogen bromide. The yield was calculated on the basis of the product obtained in the latter reaction. For identification of the imine, the *hydrochloride* of *ethyl-β-chloroethylamine*, m.p. 221–222°, was prepared by treatment of a portion of the ether solution of the imine with hydrogen chloride. Lasselle and Sundet (19) report m.p. 223° for this substance.

1-(n-Butyl-2,2-dimethylethylenimine (IX). The requisite 2-methyl-2-*n*-butylaminopropanol, b.p. 121–126° (55 mm.), was prepared either by the method of Pierce, *et al.* (31), or by the method of Cope and Hancock (32).

By treating a portion of 150 g. of the hydrochloride of this amino alcohol with 182 g. of chlorosulfonic acid and following the procedure described above there was obtained 84 g. (80%) of 1-*n*-butyl-2,2-dimethylethylenimine, b.p. 135–136°; n_D^{25} 1.4162.

Anal. Calc'd for $C_8H_{17}N$: C, 75.6; H, 13.4; N, 11.0.
Found: C, 75.3; H, 13.5; N, 11.2.

For characterization, an ether solution of the imine was treated with hydrogen chloride and a *chloroamine hydrochloride*, m.p. 209–210°, giving analytical figures for either 1-*n*-butylamino-2-chloro-2-methylpropane hydrochloride or 1-chloro-2-*n*-butylamino-2-methylpropane hydrochloride was obtained. Which of the two isomers was at hand was not determined, since regardless of which isomer was obtained, the structure assigned to the imine is corroborated.

Anal. Calc'd for $C_8H_{19}Cl_2N$: C, 48.0; H, 9.6.
Found: C, 48.0; H, 9.8.

1-n-Butyl-2-ethylethylenimine (X). Employing the method of Cope and Hancock (32), 2-aminobutanol-1 was reductively alkylated to give a 46% yield of 2-*n*-butylaminobutanol-1, b.p. 105–108° (18 mm.). From 75 g. of the crude hydrochloride of this amino alcohol 36.5 g. (70%) of 1-*n*-butyl-2-ethylethylenimine, b.p. 63–65° (55 mm.) or 137–139°; n_D^{25} 1.4152, was obtained.

Anal. Calc'd for $C_8H_{17}N$: C, 75.5; H, 13.4; N, 11.0.
Found: C, 75.4; H, 13.2; N, 10.9.

Treatment of an ether solution of the above imine with hydrogen bromide gave a *bromoamine hydrobromide*, m.p. 197–198° (from dioxane).

Anal. Calc'd for $C_8H_{19}Br_2N$: C, 33.2; H, 6.6.
Found: C, 33.2; H, 6.5.

B. AZETIDINE

1-n-Butylazetidine (VI) *picrate*. By reacting trimethylene chlorohydrin (Eastman Kodak) with *n*-butylamine in a manner similar to that of Goldberg and Whitmore (33) a 60% yield of γ-butylaminopropanol, b.p. 110–113° (18 mm.), was obtained. One hundred

twenty-eight grams of crude γ-butylaminopropanol hydrochloride was treated with 145 g. of chlorosulfonic acid. When carried through the procedure described above for the preparation of the ethylenimines, there was obtained 26 g. (30%) of a colorless liquid, b.p. 53–55° (55 mm.) or 127–128°. The *hydrobromide* of this base melted at 92–94° but was unstable on standing. The *picrate* recrystallized from benzene formed bright yellow rods m.p. 109–111° (softening 106–109°).

Anal. Calc'd for $C_{13}H_{18}N_4O_7$: C, 45.6; H, 5.3; N, 16.4.
Found: C, 45.9; H, 5.2; N, 16.4.

C. PYRROLIDINES

N-n-Butylpyrrolidine (I). A mixture of 254 g. of 1,4-dichlorobutane (5) (E.I. du Pont de Nemours & Co., Inc., material redistilled, b.p. 153–154°), 219 g. of *n*-butylamine, 138 g. of anhydrous potassium carbonate, and 200 ml. of absolute ethanol was heated on the steam-bath for sixty hours. Upon working up the reaction mixture there was obtained 133 g. (52%) of a colorless liquid b.p. 152–153° or 70–72° (45 mm.). Ochiai, Tsuda, and Yokoyama (3) report b.p. 88° (63 mm.).

1-n-Butyl-2,5-dimethylpyrrolidine (II) *hydrobromide*. When equimolar quantities of acetonylacetone and *n*-butylamine were mixed in absolute ethanol solution and allowed to stand for one hour a 90% yield of 1-*n*-butyl-2,5-dimethylpyrrole, b.p. 101–104° (22 mm.) was obtained. Bishop (34) reports b.p. 69° (4.0 mm.) for this compound prepared from the same starting materials in a slightly different manner.

Reduction of 135 g. of the above pyrrole in 200 ml. of absolute ethanol over 12 g. of Raney nickel and 2000 lbs. of hydrogen at 180–190° resulted in the absorption of the calculated amount of hydrogen during one-half hour. There was obtained 115 g. (82%) of a colorless, basic liquid, b.p. 72–74° (25 mm.). The *hydrobromide* once recrystallized from dioxane–ethanol formed white needles m.p. 173–174.5°.

Anal. Calc'd for $C_{10}H_{22}BrN$: C, 50.9; H, 9.4.
Found: C, 50.9; H, 9.6.

1-n-Butyl-2-methylpyrrolidine (III). A mixture of 141 g. of 1,4-dichloropentane (5), 73 g. of *n*-butylamine, and 138 g. of anhydrous potassium carbonate was heated on the steam-bath for fifty-five hours. After the addition of sufficient water to dissolve the solids present, the organic material was taken up in ether. The ether solution was extracted with excess dilute hydrochloric acid and then dried over calcium chloride. Eighty grams of unreacted 1,4-dichloropentane was recovered. From the acidic aqueous extracts 60 g. (43%) of a colorless liquid b.p. 74–75° (35 mm.) or 83–84° (50 mm.) was isolated. The *hydrochloride* recrystallized from acetone melted at 167–168°. Kyosuke and Tsuda (35) report b.p. 85–87° (57 mm.); hydrochloride m.p. 168° for 1-*n*-butyl-2-methylpyrrolidine.

1-n-Butyl-2,2-dimethylpyrrolidine (IV). Before the appearance of a paper by Buckley and Elliot (8) on the nature of the products obtained by the reduction of γ-methyl-γ-nitrovaleronitrile similar work was being carried out for the purpose of preparing the above pyrrolidine. Following the procedure of Bruson (36), 2-nitropropane was condensed with acrylonitrile to give a 72% yield of γ-methyl-γ-nitrovaleronitrile (XI), b.p. 105–108° (1.0 mm.). Attempts to reduce this nitronitrile using a platinum oxide catalyst either in glacial acetic acid or in absolute ethanol at 1 to 2 atmospheres of hydrogen resulted in the isolation of no definite products.

A solution of 71 g. (0.50 mol) of γ-methyl-γ-nitrovaleronitrile in 300 ml. of absolute ethanol after shaking for three hours with 6 g. of Raney nickel at 50° under 1250 lbs. of hydrogen, absorbed no hydrogen. Reduction set in at 90° and during one hour 1.1 moles of hydrogen was absorbed. No pressure drop was observed during an additional one hour of shaking. Removal of the catalyst and the ethanol (under reduced pressure) left a residue of 48 g. Addition of 150 ml. of ether to this residue followed by filtration yielded 13 g. of a white crystalline solid, m.p. 237–238°. Removal of the ether from the filtrate and distillation of the residual liquid gave 9.5 g. of a fraction of b.p. 115–120° (18 mm.). This material was not investigated.

A sample of the solid obtained, after two recrystallizations from dioxane–ethanol, gave white plates m.p. 238–239°.

Anal. Calc'd for $C_6H_{12}N_2O$: C, 56.3; H, 9.5.
Found: C, 56.2; H, 9.5.

Buckley and Elliot (8) report m.p. 238° for 1-hydroxy-5-imino-2,2-dimethylpyrrolidine (XIII).

Treatment of a methanolic solution of the above material with hydrogen chloride gave a solid *hydrochloride*, which after two recrystallizations from dioxane–ethanol formed white needles m.p. 174–175°.

Anal. Calc'd for $C_6H_{13}ClN_2O$: C, 43.8; H, 8.0.
Found: C, 43.9; H, 8.1.

Buckley and Elliot (8) report m.p. 173° for this hydrochloride.

A reduction carried out identically to that above except for the substitution of 1 g. of platinum oxide for the 6 g. of Raney nickel gave 28 g. (44%) of *1-hydroxy-5-imino-2,2-dimethylpyrrolidine*.

A solution of 141 g. (1.0 mol) of γ-methyl-γ-nitrovaleronitrile in 250 ml. of absolute methanol was heated in a bomb to 170° without shaking, in the presence of 12 g. of Raney nickel under 2200 lbs. of hydrogen. Initiation of shaking caused a rapid rise in temperature to 230°. Shaking was stopped after one minute and resumed when the temperature had fallen to 200°. Hydrogen absorption stopped after ten minutes and further shaking at 240° and 2800 lb. pressure resulted in no additional hydrogen uptake.

After removal of the catalyst and the methanol, distillation of the residue yielded 69 g. (61%) of a colorless liquid b.p. 147–148° (32 mm.) or 140–142° (26 mm.) which solidified to a hygroscopic white crystalline solid. Buckley and Elliot (8) report b.p. 140° (20 mm.) for 2,2-dimethyl-5-pyrrolidone (XII). A sample of this material when heated to 100° for three minutes with an equal weight of p-nitrobenzoyl chloride gave an alkali-insoluble solid which, after two recrystallizations from ethanol formed white needles m.p. 147–149°.

Anal. [For 1-(p-nitrobenzoyl)-2,2-dimethyl-5-pyrrolidone]
Calc'd for $C_{13}H_{14}N_2O_4$: C, 59.5; H, 5.4.
Found: C, 59.5; H, 5.2.

A duplicate reduction gave a 58% yield of this pyrrolidone.

A mixture of 104 g. (0.92 mole) of 2,2-dimethyl-5-pyrrolidone in 300 ml. of n-butanol and 13 g. of copper chromite catalyst was reduced under 2750 lbs. of hydrogen at 250°. In four hours 1 mole of hydrogen was absorbed. After filtration of the catalyst and removal of the solvent, distillation gave 45 g. of material, b.p. 175–185°. Distillation of the residue under vacuum gave a recovery of 41 g. of the starting pyrrolidone. Redistillation of the fraction b.p. 175–185° gave 39.4 g. of a colorless liquid, b.p. 176–178°; n_D^{25} 1.4380.

Anal. Calc'd for $C_{10}H_{21}N$: C, 77.3; H, 13.6.
Found: C, 76.9; H, 13.8.

The *hydrobromide* of the pyrrolidine was recrystallized from dioxane and formed long white needles, m.p. 148–149.5°.

Anal. Calc'd for $C_{10}H_{22}BrN$: C, 50.9; H, 9.4; N, 5.9.
Found: C, 50.9; H, 9.3; N, 5.9.

Calculated on the basis of recovered pyrrolidone the yield of 1-n-butyl-2,2-dimethylpyrrolidine was 45%.

1-Isopropyl-2-methylpyrrolidine (V). This material, b.p. 140–142°, was prepared in 26% yield by refluxing, for two days, a mixture of 1 mole of 1,4-dichloropentane (5) and 3 moles of isopropylamine. A sample of b.p. 140°; n_D^{25} 1.4350 was taken for analysis.

Anal. Calc'd for $C_8H_{17}N$: C, 75.7; H, 13.4.
Found: C, 75.3; H, 13.5.

The *hydrobromide*, m.p. 193–194°, was recrystallized from dioxane–ethanol mixture.

Anal. Calc'd for $C_8H_{18}BrN$: C, 46.2; H, 8.7.
Found: C, 46.4; H, 9.0.

II. REACTION OF THE NITROGEN HETEROCYCLES WITH CYANOGEN BROMIDE.

The *cyanogen bromide* used was prepared following the procedure of Hartman and Dreger (37).

With 1-n-butylpyrrolidine. To a solution of 59 g. (0.55 mole) of cyanogen bromide in 300 ml. of dry benzene a solution of 60 g. (0.47 mole) of 1-*n*-butylpyrrolidine in 300 ml. of dry benzene was added from a dropping-funnel with stirring during two and one-half hours. During the addition the solution remained clear and remained at a temperature of 35–40°. After standing overnight the mixture was extracted with 200 ml. of 5% hydrochloric acid and then with two 100-ml. portions of water. After drying the benzene solution over calcium chloride and removing the benzene (finally under water-pump vacuum at 90°), there remained 110 g. of a clear amber-colored liquid. The theoretical yield of *n*-butyl-δ-bromobutylcyanamide is 110 g.

A portion of 64 g. of this material was distilled through a 6-inch vacuum-jacketed Vigreux column yielding 36 g. of distillate b.p. 136–138° (1.0 mm.). Ochiai, Tsuda, and Yokoyama (3) report b.p. 120° (0.01 mm.) for this material. The residue in the distilling flask, which had been darkening slowly, turned to a thick, gummy mass and rapid decomposition set in. The possibility of securing satisfactory purification by distillation at a higher vacuum was not investigated.

The remainder (46 g.) of the crude reaction product was refluxed for three hours with 110 g. of diethylamine. Separation of a large amount of solid material began immediately. A solution of 20 g. of potassium hydroxide in 30 ml. of water was added and the excess diethylamine was removed under reduced pressure. Sufficient water was added to the residue to dissolve the potassium bromide and the brown oil was taken up in 250 ml. of ether and dried over potassium carbonate. Removal of the ether gave 41 g. (91%) of residue which, when distilled through a 6-inch vacuum-jacketed Vigreux column, gave 37 g. (82%) of *n*-butyl-δ-diethylaminobutylcyanamide, b.p. 125–126° (0.5 mm.). An *oxalate* recrystallized from dioxane formed white needles m.p. 93–96° (softening 88°).

Anal. Calc'd for $C_{15}H_{29}N_3O_4$: C, 57.1; H, 9.2.

Found: C, 56.8; H, 9.4.

A subsequent run using 138 g. (0.59 mole) of the crude bromocyanamide and 130 g. (2.06 moles) of diethylamine gave 120 g. (91%) of the distilled diethylamino derivative (XV), b.p. 128–130° (0.7 mm.). When a sample of 20 g. of this material was refluxed for fourteen hours with a solution of 40 g. of sulfuric acid in 120 ml. of water, there was isolated 14.2 g. (80%) of a liquid b.p. 135–137° (26 mm.); n_D^{25} 1.4418. A *dihydrobromide* melted at 168–170°. This material is *1-diethylamino-4-butylaminobutane.* Analytical data for the substance are listed under a later experiment.

With 1-n-butyl-2,5-dimethylpyrrolidine. In the manner described above, a solution of 62 g. (0.40 mole) of 1-*n*-butyl-2,5-dimethylpyrrolidine in 300 ml. of dry benzene was added, over two hours to a solution of 44.6 g. (0.44 mole) of cyanogen bromide in 300 ml. of dry benzene. A clear yellow solution resulted which was allowed to stand overnight. After washing the benzene solution with dilute acid and water, as previously described, the benzene solution was dried over calcium chloride. Removal of the benzene (finally under water-pump vacuum at steam-bath temperature) yielded 94 g. of a red-brown oil. The theoretical yield of *butyl-(1-methyl-4-bromoamyl)cyanamide* (XVI) is 100 g. This material was not purified.

When a solution of 50 g. (0.20 mole) of the above substance in 124 g. (1.70 moles) of diethylamine stood for sixty hours at room temperature, only a very slight amount of solid salts was formed. Refluxing for three hours caused no noticeable reaction. After standing for two weeks at room temperature a moderate amount of precipitated solid gradually formed. Removal of the excess diethylamine and treatment of the residue with excess 5% hydrochloric acid caused the separation of an acid-insoluble oil which was taken up in ether and dried over calcium chloride. Removal of the ether yielded 35 g. of a red-brown oil which was presumably recovered starting material. There was isolated 7.8 g. of a basic product b.p. 130–131° (0.6 mm.). This material was not characterized.

A sample of 25.0 g. (0.10 mole) of the crude reaction product was refluxed for three hours with 73 g. (1.0 mole) of diethylamine. The diethylamine was removed, finally under reduced pressure, the residue was treated with excess dilute hydrochloric acid, the insoluble oil was taken up in 200 ml. of ether, washed with 50 ml. of water and dried over calcium chloride. Removal of the ether and subjection of the residue to aspirator vacuum on the steam-bath for ten minutes, gave 24.1 g. (96.4% recovery) of a red-brown oil.

A mixture of 56 g. (0.21 mole) of crude bromocyanamide and 13 g. (0.23 mole) of potassium hydroxide in 200 ml. of absolute ethanol was refluxed for one and one-half hours and then cooled and filtered to remove the potassium bromide. Removal of the ethanol from the filtrate and treatment of the residue with 50 ml. of water yielded an oil which was taken up in ether and dried over magnesium sulfate. Removal of the ether and distillation of the residue gave 34.9 g. (91%) of a colorless liquid (XVII) b.p. 108–110° (1.9 mm.); n_D^{25} 1.4518.

Anal. Calc'd for $C_{11}H_{20}N_2$: C, 73.3; H, 11.2.

Found: C, 73.3; H, 11.4.

Reduction of 33.9 g. of this unsaturated cyanamide in 150 ml. of absolute ethanol using 0.5 g. of palladium black at 2 to 3 atmospheres of hydrogen resulted in the theoretical hydrogen uptake during forty-five minutes. Removal of the catalyst and the ethanol left a pale yellow liquid which was dissolved in 200 ml. of ether and extracted with 60 ml. of 5% hydrochloric acid, then with 60 ml. of water. Drying over calcium chloride, removal of the ether, and distillation of the residue gave 28.1 g. (83%) of a colorless liquid (XVIII) b.p. 103–105° (1.5 mm.); n_D^{25} 1.4390.

Anal. Calc'd for $C_{11}H_{22}N_2$: C, 72.5; H, 12.2.

Found: C, 72.5; H, 12.1.

A sample of 27.1 g. of this cyanamide was refluxed for twenty hours with a solution of 57 g. of sulfuric acid in 170 ml. of water. The cooled solution was made strongly alkaline with potassium hydroxide and extracted with three 100-ml. portions of ether. After drying over potassium carbonate, the ether was removed and the residue distilled. There was collected 21.2 g. (74%) of *2-n-butylaminohexane* b.p. 92–94° (30 mm.). The *hydrochloride* was recrystallized from acetone as fine, white rods m.p. 140–141.5°.

Anal. Calc'd for $C_{10}H_{24}ClN$: C, 62.0; H, 12.5.

Found: C, 62.3; H, 12.7.

An authentic sample of 2-*n*-butylaminohexane, prepared in 66% yield by the catalytic reduction of equimolar quantities of hexanone-2 and *n*-butylamine in ethanol solution using platinum oxide and three atmospheres of hydrogen boiled at 85–87° (24 mm.). The *hydrochloride* was recrystallized from acetone and formed fine white rods m.p. 139–140.5°. A mixed melting point of the two samples was 139.5–141°.

Separation of a mixture of n-butyl-δ-bromobutylcyanamide and n-butyl-(1-methyl-4-bromoamyl)cyanamide by reaction with diethylamine. The materials used were the crude products obtained from the ring opening of the respective pyrrolidines with cyanogen bromide.

A mixture of 50.3 g. (0.192 mole) of XVI and 40.2 g. (0.172 mole) of XIV in 266 g. (3.64 moles) of diethylamine (distilled over sodium) was refluxed for three hours. Removal of the excess diethylamine, under vacuum, using a large bore capillary, left a residue which was treated with sufficient 10% hydrochloric acid to yield a definitely acidic aqueous portion. The acid-insoluble oil was taken up in 300 ml. of ether, extracted with 50 ml. of water and dried over calcium chloride.

The acidic aqueous portion, to which had been added the 50 ml. of wash water, was made strongly alkaline with potassium hydroxide and extracted with two 200-ml. portions of ether and the combined ether extracts were dried over potassium carbonate.

Removal of the ether from the solution of the non-basic material (finally under water-pump vacuum at steam-bath temperature) left as residue 47.8 g. of an amber colored oil. This corresponds to a recovery of 95% of XVI.

Removal of the ether from the solution of the basic product (finally at 23 mm. and 80° for ten minutes) gave 38.3 g. (99%) of *butyl-δ-diethylaminobutylcyanamide*. Upon distillation this gave 34.8 g. of material; b.p. 128–130° (0.6 mm.).

With 1-n-butyl-2-methylpyrrolidine. Addition, over four hours, of a solution of 70.5 g. (0.50 mole) of 1-*n*-butyl-2-methylpyrrolidine in 200 ml. of benzene to a stirred solution of 58.2 g. (0.55 mole) of cyanogen bromide in 200 ml. of benzene gave a clear, pale yellow solution which was allowed to stand overnight. Extraction of this benzene solution with 100 ml. of 5% hydrochloric acid was followed by extraction with two 100-ml. portions of water. Drying over calcium chloride and removal of the benzene under reduced pressure left as residue 120 g. of a clear, red-brown liquid. The theoretical yield of ring-opened product is 123 g.

This crude product (120 g., 0.49 mole), suspected of being a mixture of isomers, was refluxed for three and one-half hours with 292 g. (4.0 mols) of diethylamine. After removal of the excess diethylamine the residue was treated with a solution of 50 ml. of concentrated hydrochloric acid in 200 ml. of water. The acid-insoluble oil was taken up in 350 ml. of ether and dried over calcium chloride. Removal of the ether left 31.9 g. of a yellow liquid. As shown below, this is the isomer (XX) containing the secondary alkyl bromide.

The above acidic aqueous solution was made strongly alkaline with potassium hydroxide. The oil which separated was taken up in 400 ml. of ether and dried over potassium carbonate. Removal of the ether and traces of diethylamine left, as residue, 81.0 g. of a clear, red-brown liquid.

In another experiment 60 g. of crude ring-opened product similarly treated with diethylamine gave 15.5 g. of non-basic material and 40.7 g. of the basic diethylamino derivative (XXI).

Distillation of 40.7 g. of this crude basic product gave 35.8 g. of a pale yellow oil b.p. 130–133° (0.7 mm.). The *oxalate*, on recrystallization from dioxane formed thin white needles m.p. 103–105° (shrinks 101–103°).

Anal. Calc'd for $C_{16}H_{31}N_3O_4$: C, 58.3; H, 9.5.
Found: C, 58.4; H, 9.6.

A sample of 15.0 g. of the above liquid, b.p. 130–133° (0.7 mm.) was refluxed five hours with a solution of 20 g. of sulfuric acid in 40 ml. of water. After making this solution alkaline, extracting with ether, drying over potassium carbonate, and removing the ether, distillation of the residue gave 11.5 g. (86%) of a colorless liquid (XXII) b.p. 125–126° (14 mm.). The *dihydrochloride* was recrystallized from acetone as white needles m.p. 201–203°.

Anal. Calc'd for $C_{13}H_{32}Cl_2N_2$: C, 54.3; H, 11.2; N, 9.7.
Found: C, 54.7; H, 11.2; N, 9.4.

Alkylation of a sample of Novol diamine (1-diethylamino-4-aminopentane), b.p. 85–86° (20 mm.) (purified *via* the dithiocarbamate) with *n*-butyl bromide gave a 47% yield of 1-diethylamino-4-*n*-butylaminopentane b.p. 136–138° (22 mm.). The *hydrochloride* formed white needles, m.p. 201–203°, from acetone. A mixed melting point with the above material gave m.p. 201–203°.

Treatment of a sample of the *n*-butyl-Novol diamine with cyanogen bromide gave in low (15%) yield a pale yellow liquid b.p. 128–130° (0.5 mm.). The *oxalate* after one recrystallization from acetone formed thin, white needles m.p. 103–105° (shrinks 100–103°). A mixed melting point of this material with the oxalate derived from the ring-opened product was 103–105° (shrinks 100–103°).

The isomer in the crude reaction mixture obtained from the ring-opening reaction, which did not react with diethylamine, was treated as follows:

A sample of 31.9 g. (0.13 mole) of this material was refluxed for one and one-half hours with a solution of 7.3 g. of potassium hydroxide in 125 ml. of absolute ethanol. After cooling in an ice-bath, the potassium bromide was removed by filtration. The ethanol was removed from the filtrate, the residue treated with 30 ml. of water, and the insoluble oil taken up in 100 ml. of ether and dried over magnesium sulfate. Removal of the ether and distillation of the residual brown liquid gave 19.2 g. (90%) of a colorless liquid b.p. 85–87° (0.5 mm.).

Reduction of 18.4 g. of this unsaturated material in 150 ml. of absolute ethanol using

0.4 g. of palladium black and 2 atmospheres of hydrogen resulted in the absorption of the theoretical amount of hydrogen at the end of one hour. Removal of the catalyst and ethanol and distillation of the residue gave 15.8 g. (85%) of a colorless liquid b.p. 90–92° (0.8 mm.).

Refluxing 14.6 g. of this material with a solution of 40 g. of sulfuric acid in 120 ml. of water for twenty hours and working up, as previously described, gave 11.4 g. of a brown liquid. Upon distillation over sodium there was collected 7.8 g. (63%) of colorless *butylamylamine* (XXIII) b.p. 80–81° (24 mm.); n_D^{20} 1.4220; n_D^{25} 1.4192. Henze and Humphreys (38) report b.p. 180–182° (743 mm.); n_D^{20} 1.4230 for butylamylamine.

The *picrolonate* formed pale yellow needles m.p. 215.5–216° from ethanol.

By the alkylation of *n*-butylamine with *n*-amyl bromide a sample of butylamylamine b.p. 81–82° (26 mm.); n_D^{25} 1.4190 was obtained.

The *picrolonate* formed pale yellow needles m.p. 215.5–216° from ethanol and showed no depression when mixed with the above picrolonate.

Anal. Calc'd for $C_{19}H_{29}N_5O_5$: N, 17.7. Found: N, 17.5.

With 1-isopropyl-2-methylpyrrolidine. The addition of 33.0 g. (0.26 mole) of this pyrrolidine in 150 ml. of benzene to a solution of 30.0 g. (0.28 mole) of cyanogen bromide in 200 ml. of benzene over four hours gave, after working up in the manner previously described, 57.0 g. (94%) of crude reaction product consisting of an amber-colored liquid. This was refluxed four hours with 146 g. of diethylamine. There was isolated 18.4 g. of an acid-insoluble amber-colored liquid assumed to be the ring-opened product containing the secondary alkyl bromide. No work was done to establish the structure of this material.

There was isolated 36.1 g. of basic material consisting of a brown liquid. When twice distilled, 30.7 g. of a pale yellow liquid b.p. 107–110° (0.4 mm.) was collected. An *oxalate* was recrystallized from dioxane–ethanol as fine white needles m.p. 132–134° (dec.).

Anal. Calc'd for $C_{15}H_{29}N_3O_4$: C, 57.1; H, 9.3.
Found: C, 57.3; H, 9.1.

Though no work was done to prove definitely the structure of this material, it is assumed to be *1-diethylamino-4-(isopropylcyanamido)pentane* (XXVI).

With 1-n-Butyl-2,2-dimethylpyrrolidine. There was added, over five hours with stirring, a solution of 49.3 g. (0.320 mole) of 1-*n*-butyl-2,2-dimethylpyrrolidine in 150 ml. of absolute ether to a solution of 33.9 g. (0.320 mole) of cyanogen bromide in 200 ml. of absolute ether. When the addition was approximately one-half complete, the clear solution became cloudy and a small quantity of a white crystalline solid began to separate. The amount of this steadily increased during the remainder of the addition. After standing overnight at room temperature, the mixture was filtered and the solid washed with ether yielding 21.0 g. of a white crystalline solid m.p. 145–147°. Recrystallization of a sample from dioxane gave white needles m.p. 148–149°. A mixed m.p. showed this to be the *hydrobromide* of *1-n-butyl-2,2-dimethylpyrrolidine*.

Extraction of the ether solution with two 60-ml. portions of water gave a neutral aqueous solution, which after making strongly basic, was extracted with ether. After drying these combined ether extracts over potassium hydroxide, removal of the ether left 3.8 g. of a colorless basic liquid.

After extracting the ether solution of the original reaction mixture with 100 ml. of 7% hydrochloric acid followed by extraction with two 100-ml. portions of water, it was dried over magnesium sulfate. By making these acidic aqueous extracts basic and extracting with ether there was obtained 6.1 g. more of a basic liquid. Distillation of the total of 9.9 g. of this base gave 7.2 g. of a colorless liquid b.p. 74–76° (22 mm.). Total recovery of the starting material in the form of the hydrobromide and the free base amounted to 0.136 mole.

Removal of the ether from the solution of the non-basic product left as residue 30.0 g. of an amber-colored liquid, which, upon distillation, gave 24.3 g. of a yellow liquid b.p. 108–111° (1.3 mm.). This, upon standing overnight, turned to a clear red-brown liquid.

This 24.3 g. (0.135 mole., assuming it to be an unsaturated cyanamide) in 150 ml. of

absolute ethanol was hydrogenated at three atmospheres pressure, over 0.5 g. of palladium black. After shaking for three hours, the calculated amount of hydrogen was absorbed. When removed from the shaker, an ammoniacal odor was noticed. Removal of the catalyst and ethanol yielded 24.4 g. of a yellow liquid, which was dissolved in 150 ml. of ether and extracted with 100 ml. of 7% hydrochloric acid and then with 50 ml. of water. After drying over calcium chloride and removing the ether, 16.5 g. of an amber-colored liquid was obtained. Distillation of this gave 13.0 g. of a colorless liquid b.p. 101–103° (1.0 mm.). A cut of b.p. 102° (1.0 mm.); n_D^{25} 1.4450 was taken for analysis.

Anal. Calc'd for $C_{11}H_{22}N_2$: C, 72.5; H, 11.6.
Found: C, 72.4; H, 11.6.

This material is *n-butylisohexylcyanamide* (XXXI).

A sample of 11.9 g. of this cyanamide was hydrolyzed by refluxing for twenty hours with a solution of 25 g. of sulfuric acid in 75 ml. of water. Upon working up this mixture, there was obtained 7.1 g. of *n-butylisohexylamine* (XXXII) b.p. 94–96° (28 mm.). The *hydrochloride*, twice recrystallized from acetone, formed colorless plates m.p. 279–280° (darkens 276–278°).

Anal. Calc'd for $C_{10}H_{24}ClN$: C, 62.0; H, 12.5.
Found: C, 62.1; H, 12.5.

A sample of *n-butylisohexylamine*, prepared by the alkylation of isohexylamine (b.p. 122–125°) with *n*-butyl bromide, gave b.p. 87–88° (20 mm.). The *hydrochloride* formed colorless plates m.p. 276–277° (darkens 272–274°) from acetone. A mixed melting point of this material with that above was 276–278° (darkens 272–276°).

A *second* ring opening of 1-*n*-butyl-2,2-dimethylpyrrolidine with cyanogen bromide was carried out as follows:

A solution of 34.3 g. (0.22 mole) of 1-*n*-butyl-2,2-dimethylpyrrolidine in 150 ml. of dry benzene was added over three hours, with stirring to a solution of 27.0 g. (0.25 mole) of cyanogen bromide in 150 ml. of benzene. The resulting clear yellow benzene solution was refluxed for fifteen minutes and allowed to stand overnight at room temperature. After extracting with 100 ml. of 5% hydrochloric acid and two 100-ml. portions of water, the benzene solution was dried over calcium chloride.

From these acidic aqueous extracts there was recovered 15.2 g. (0.10 mole) of 1-butyl-2,2-dimethylpyrrolidine b.p. 63–65° (14 mm.).

Removal of the benzene from the above solution of non-basic products left 21.0 g. of a light amber-colored liquid which was refluxed for three hours with 58 g. of diethylamine and allowed to stand overnight. The formation of no solid salts was noticed. Removal of the diethylamine left a dark red-brown liquid which was treated with excess dilute hydrochloric acid. The acid-insoluble liquid was taken up in ether and dried over magnesium sulfate. Removal of the ether left 17.8 g. of a red-brown liquid which gave on distillation 14.2 g. of a clear yellow liquid b.p. 91–95° (0.45 mm.) which turned to a red-brown color on standing overnight. This 14.2 g. (0.08 mole) of unsaturated cyanamide together with the 15.2 g. (0.10 mole) of recovered starting material accounts for 0.18 mole of the 0.22 mole of starting material. By making the acidic extracts of the product resulting from the reaction with diethylamine basic and extracting with ether, there was isolated 0.2 g. of a dark oil which was discarded.

With 1-n-butylazetidine. Addition, over three hours with stirring, of a solution of 18.5 g. (0.16 mole) of 1-*n*-butylazetidine in 150 ml. of absolute ether to a solution of 17.4 g. (0.16 mole) of cyanogen bromide in 200 ml. of absolute ether gave a clear, pale yellow solution which was allowed to stand overnight at room temperature. After extracting with 100 ml. of 5% hydrochloric acid and two 50-ml. portions of water, the ether solution was dried over magnesium sulfate. Removal of the ether left 35.1 g. of a pale yellow liquid which gave, on distillation, 30.7 g. (85%) of a colorless liquid b.p. 110–112° (0.4 mm.); n_D^{25} 1.4778. A sample on redistillation gave b.p. 115–116° (0.7 mm.); n_D^{25} 1.4783.

Anal. Calc'd for $C_8H_{15}BrN_2$: C, 43.9; H, 6.9.
Found: C, 43.8; H, 6.6.

A solution of 10.8 g. of this material in 50 g. of diethylamine was allowed to stand for

twenty hours at room temperature. A copious precipitate of solid salts formed. After removing the excess diethylamine under water-pump vacuum, the residue was treated with excess aqueous potassium hydroxide and extracted with three 50-ml. portions of ether. After drying the combined ether extracts over potassium carbonate, the ether and traces of diethylamine were removed under reduced pressure, leaving 11.0 g. of a straw-colored liquid. Distillation gave 8.7 g. (83%) of a pale yellow liquid b.p. 108–110° (0.4 mm.). This material is *n-butyl-γ-diethylaminopropylcyanamide*. An *oxalate* formed white needles m.p. 131–132.5° (dec.) from acetone.

Anal. Calc'd for $C_{14}H_{27}N_3O_4$: C, 55.8; H, 9.0.
Found: C, 55.9; H, 9.3.

With 1-n-butylethylenimine. When a solution of 65 g. (0.65 mole) of 1-n-butylethylenimine in 300 ml. of absolute ether was added over four hours, with stirring, to a solution of 75 g. (0.71 mole) of cyanogen bromide in 200 ml. of ether, the heat of reaction was sufficient to maintain gentle refluxing of the ether. After standing overnight, the clear pale yellow ether solution was extracted with 100 ml. of 5% hydrochloric acid and two 100-ml. portions of water and then dried over calcium chloride. Removal of the ether and distillation of the residue (131 g.) gave 126 g. (94%) of a colorless liquid b.p. 106–108° (0.6 mm.). A middle cut b.p. 106–107° (0.6 mm.); n_D^{25} 1.4804 was taken for analysis.

Anal. Calc'd for $C_7H_{13}BrN_2$: C, 41.0; H, 6.4; N, 13.7.
Found: C, 41.1; H, 6.2; N, 13.7.

A sample of 20.5 g. of this material was refluxed for three hours with 73 g. of diethylamine. The formation of a large amount of solid amine salts took place rapidly. After standing overnight at room temperature, the excess diethylamine was removed and excess aqueous potassium hydroxide was added. Extraction with ether, drying over potassium carbonate and removal of the ether and distillation of the residue gave 14.0 g. (71%) of a colorless liquid b.p. 98–110° (0.4 mm.). An *oxalate*, recrystallized from dioxane–isopropanol (3:1), formed clusters of short, white needles m.p. 95–96° (dec.).

Anal. Calc'd for $C_{13}H_{25}N_3O_4$: C, 54.3; H, 8.8.
Calc'd for $[C_{13}H_{25}N_3O_4]_2 \cdot C_3H_8O$: C, 54.9; H, 9.3.
Found: C, 54.8; H, 9.2.

With 1-ethylethylenimine. Addition over six hours of a solution of 71 g. (1.0 mole) of 1-ethylethylenimine in 300 ml. of ether to a solution of 106 g. (1.0 mole) of cyanogen bromide in 300 ml. of ether gave, after working up as above 156 g. (88%) of a colorless liquid b.p. 92–94° (0.6 mm.); n_D^{20} 1.4864. Redistillation of a sample gave b.p. 89–90° (0.4 mm.); n_D^{25} 1.4862.

Anal. Calc'd for $C_5H_9BrN_2$: C, 33.9; H, 5.1.
Found: C, 34.2; H, 5.3.

With 1-n-butyl-2,2-dimethylethylenimine. Over a period of seven hours there was added, with stirring, a solution of 80.0 g. (0.62 mole) of 1-n-butyl-2,2-dimethylethylenimine in 300 ml. of absolute ether to solution of 65 g. (0.62 mole) of cyanogen bromide in 300 ml. of ether. Approximately one hour after the addition was started a small amount of a white, crystalline solid began to precipitate. This slowly increased in quantity during the remainder of the addition. After standing overnight the reaction mixture consisted of a yellow solution and a precipitated tan solid. Addition of 250 ml. of absolute ether caused the precipitation of more solid. Filtration of the mixture and washing the collected solid with ether gave a slightly sticky light brown solid. Addition of 400 ml. of absolute ether to a solution of this in 40 ml. of absolute alcohol caused the precipitation of a white, crystalline solid. The collected solid was washed with ether yielding 28.0 g. (0.10 mole) of white plates m.p. 192.5–193.5°. A mixed melting point with the material of m.p. 192.5–193.5°, obtained by treating 1-n-butyl-2,2-dimethylethylenimine with hydrogen bromide, showed no depression. Recrystallization from dioxane of a sample of the material obtained from the reaction mixture gave white plates m.p. 193.5–194.5°.

Anal. Calc'd for $C_8H_{19}Br_2N$: C, 32.2; H, 6.6.
Found: C, 32.1; H, 6.7.

After extracting the ether filtrate from the above solid with 100 ml. of 5% hydrochloric

acid and then with two 100-ml. portions of water, it was dried over calcium chloride. Removal of the ether left 84 g. of a clear amber-colored liquid which gave upon distillation 27 g. of a colorless liquid b.p. 81–83° (0.9 mm.). At this stage the material in the distilling flask darkened and resinified. The distillation was stopped at this point and the hardened residue (52 g.) was saved. The above colorless liquid turned yellow on standing overnight. Redistillation gave 19.9 g. of a colorless liquid b.p. 68–69° (0.4 mm.); n_D^{28} 1.4518.

Anal. Calc'd for $C_9H_{16}N_2$: C, 71.0; H, 10.6.

Found: C, 71.1; H, 11.0.

There remained in the distilling flask from the second distillation 6.1 g. of an amber-colored gum. This indicates that this unsaturated cyanamide has a tendency to polymerize on heating.

When 19.8 g. (0.13 mole) of the distilled unsaturated cyanamide in 200 ml. of absolute methanol was shaken under 33 lbs. of hydrogen with 0.4 g. of palladium black for one hour absorption of one-third of the calculated amount of hydrogen and apparent cessation of any further uptake occurred. Addition of 0.4 g. more of palladium black and shaking for forty-five minutes resulted in the absorption of the calculated amount of hydrogen. After removing the catalyst and the methanol, there was obtained 19.7 g. of a yellow liquid. After adding 60 ml. of 5% hydrochloric acid, the mixture was extracted with two 60-ml. portions of ether and these extracts were dried over calcium chloride. When the acidic aqueous portion was made alkaline, 2 to 3 g. of a basic liquid separated. This material was not investigated.

Removal of the ether from the solution of the non-basic material left 15.7 g. of a yellow liquid. Distillation gave 13.8 g. of a colorless liquid b.p. 74–75° (0.8 mm.); n_D^{25} 1.4382.

Anal. Calc'd for $C_9H_{18}N_2$: C, 70.1; H, 11.7.

Found: C, 70.3; H, 11.1.

A sample of 13.4 g. of this material, assumed to be *butylisobutylcyanamide*, was refluxed for twenty hours with a solution of 40 g. of sulfuric acid in 120 ml. of water. Upon working up, as in previous examples, 9.0 g. of a pale yellow liquid was obtained. Distillation over sodium gave 6.6 g. of a colorless liquid b.p. 147–148°; $n_D^{20°}$ 1.4125. Henze and Humphreys (38) report b.p. 150–151° (738 mm.); $n_D^{20°}$ 1.4120 for *butylisobutylamine*. The *phenylthiourea* prepared from this was recrystallized from ethanol-water giving colorless rhombohedra m.p. 83–84.5° (softens 82–83°). A mixture of this phenylthiourea with a sample prepared from a known sample of butylisobutylamine melted at 83–84.5° (softens 82–83°).

Anal. Calc'd for $C_{15}H_{24}N_2S$: C, 68.1; H, 9.1.

Found: C, 67.7; H, 8.8.

From the total of 84 g. of non-basic products there was isolated 27 g. of an unsaturated cyanamide and 52 g. of a non-distillable gum. Treatment of an ethanolic solution of this gum with ethanolic potassium hydroxide resulted in the precipitation of a considerable amount of potassium bromide but there was isolated only a viscous material which would not distill under a pressure of 0.8 mm. and a bath temperature of 230°. This material was discarded.

When a ring-opening reaction was carried out in benzene solution employing 40.0 g. of the 1-*n*-butyl-2,2-dimethylethylenimine and 37.0 g. of cyanogen bromide, there was isolated 17.0 g. of solid m.p. 192.5–193.5° and 44.5 g. of a non-basic liquid which, on distillation gave 17.3 g. of the unsaturated cyanamide b.p. 79–81° (0.7 mm.) and 23.0 g. of a residual gum.

With 1-n-butyl-2-ethylethylenimine. A solution of 35.0 g. (0.28 mole) of 1-*n*-butyl-2-ethylethylenimine in 250 ml. of absolute ether was added, with stirring, over eight hours to a solution of 33.0 g. (0.31 mole) of cyanogen bromide in 200 ml. of ether. Approximately one-half of the addition was complete when a small amount of a white solid began to precipitate. After standing overnight, the mixture was filtered from 4.2 g. of a white solid of m.p. 185–190°. A sample of the solid after one recrystallization from dioxane formed white plates m.p. 197–198°. No depression was observed on melting a mixture of this material and the *bromoamine hydrobromide* m.p. 197–198° obtained by treating 1-*n*-butyl-2-ethylethylenimine with hydrogen bromide in ether solution.

The ether filtrate from the above hydrobromide was extracted with three 50-ml. portions of water and then dried over magnesium sulfate. Evaporation of the combined aqueous extracts to dryness left 4.0 g. of an amber-colored semi-solid gum. This constitutes a total of 8.2 g. of water-soluble material obtained from the reaction mixture.

Removal of the ether from the above solution left 54.6 g. of an amber-colored liquid. Distillation of 14.0 g. of this material gave, after 2.1 g. of a forerun b.p. 73–107° (0.4 mm.), 9.5 g. of a colorless liquid of b.p. 107–109° (0.4 mm.). There remained 2.0 g. of a non-distillable, dark brown residue. On refluxing 40.6 g. of the crude product for seven hours with 73 g. of diethylamine and allowing the mixture to stand overnight, only traces of solid salts were formed. After removing the excess diethylamine and making the residue acidic with dilute hydrochloric acid, it was extracted with three 50-ml. portions of ether. After drying the ether extracts, containing the non-basic material, over magnesium sulfate, removal of the ether left 36.0 g. of an amber-colored liquid. Distillation gave 6.0 g. of a forerun b.p. 75–110° (0.4 mm.) and 24.5 g. (38%) of a colorless liquid b.p. 108–110° (0.5 mm.) which slowly darkened on standing. Redistillation of 15 g. of this material gave 8.8 g. of a colorless liquid of b.p. 106° (0.5 mm.); n_D^{25} 1.4792.

Anal. Calc'd for $C_9H_{17}BrN_2$: C, 46.4; H, 7.3; N, 12.0.
Found: C, 46.3; H, 7.4; N, 12.1.

This material is a *bromocyanamide* which did not react with diethylamine under the above conditions. The only basic product obtained from the treatment with diethylamine consisted of 2.0 g. of a dark brown liquid which was not investigated.

TABLE I

RING OPENING OF 1-*n*-BUTYL-2-ETHYLETHYLENIMINE

IMINE USED, G.	UNSATURATED CYANAMIDE, G.	SALT OF M.P. 197–198°, G.	CRUDE BROMO-CYANAMIDE, G.
35.0	5.7	4.2	49
36.8	4.9	6.1	54
57.0	8.6	6.4	87
70.0	9.7	9.0	105

The combined foreruns (8.1 g.) of b.p. 73–107° (0.4 mm.) and 75–110° (0.4 mm.) were redistilled, and 5.7 g. of a colorless liquid b.p. 73–75° (0.6 mm.); $n_D^{25°}$ 1.4510, was collected.

Anal. Calc'd for $C_9H_{16}N_2$: C, 71.1; H, 10.5.
Found: C, 70.8; H, 10.3.

This material decolorized bromine water and dilute aqueous potassium permanganate. It must be an unsaturated cyanamide resulting from an elimination reaction which furnished the hydrogen bromide required for the formation of the bromoalkylamine hydrobromide which was isolated.

Table I shows the quantities of the various products obtained from four ring openings carried out in an identical manner.

The values given for the crude bromocyanamide are those calculated by subtracting the quantity of unsaturated cyanamide obtained from the crude yield of non-basic material.

The combined unsaturated cyanamide from three runs was redistilled, giving 16.6 g. of material b.p. 75–77° (0.7 mm.); n_D^{25} 1.4491. Hydrogenation of this material in 200 ml. of methanol, over 0.5 g. of palladium black under two to three atmospheres of hydrogen resulted in absorption of 90% of the calculated amount of hydrogen after shaking for two hours. Shaking for an additional hour caused no further absorption of hydrogen. After removing the catalyst and methanol, the residue was refluxed for twenty hours with a solution of 40 g. of sulfuric acid in 120 ml. of water. Working up this hydrolysis product as in the above cases gave, after two distillations over sodium, 4.8 g. (34%) of a colorless amine of b.p. 154–156°; n_D^{25} 1.4116. A *phenylthiourea* (from ethanol–water) melted at 83–84° and a mixed melting point with the phenylthiourea, m.p. 83–84°, of di-*n*-butylamine

(b.p. 157–158°; n_D^{25} 1.4141) showed no depression. Suggitt and Wright (39) report m.p. 85.5–86° for the phenylthiourea of di-*n*-butylamine.

In an attempt to remove the bromine from the bromoalkyl cyanamide of b.p. 110–112° (0.5 mm.) for the purpose of structure identification, the following results were obtained: To a solution of 23.3 g. (0.10 mole) of the bromodibutylcyanamide in 200 ml. of absolute methanol was added 20 g. of Raney nickel (wet with ethanol). Shaking under 2 to 3 atmospheres of hydrogen resulted in the uptake of 0.10 mole of hydrogen over forty minutes. After filtering off the catalyst and distilling off the methanol at atmospheric pressure, the residue was treated with 60 ml. of 20% aqueous potassium hydroxide. The insoluble oil was taken up in 150 ml. of benzene. After distilling off the benzene (and traces of water) under atmospheric pressure, the residual brown liquid (15 g.) was distilled over sodium. After collecting 2.0 g. of a colorless liquid b.p. 55–110° (25 mm.) and 2.5 g. b.p. 110–123° (25 mm.), there was obtained 7.2 g. of a colorless distillate b.p. 123–125° (25 mm.). A residue in the distilling flask of approximately 5 g. of a light brown solid remained. Another reduction carried out similarly gave 6.8 g. of product b.p. 123–125° (25 mm.). This material was slightly water soluble, yielding a strongly basic solution. It was completely soluble in dilute acid. Redistillation of these combined products gave 11.2 g. of distillate b.p. 123–125° (25 mm.); n_D^{25} 1.4598. The substance was extremely hygroscopic and gained weight even during weighing of an analytical sample in a fine capillary. However, all available data support the structure assigned to it. If the found analytical data are corrected on the basis of the assumption that the failure of the carbon, hydrogen, and nitrogen found to add up to 100% is due to water acquired during weighing the sample, the figures obtained are consistent with calculated ones.

Anal. Calc'd for $C_9H_{18}N_2$: C, 70.1; H, 11.8; N, 18.2.
Found: C, 68.7; H, 12.0; N, 17.6.

If these figures are corrected to take into account 1.7% of water necessary to make them total 100%, the following are obtained:

Found (corr.): C, 70.0; H, 12.0; N, 17.9.
Neutral equiv.: Calc'd, 154. Found, 150.

The substance can hardly have a structure other than one of the two assigned to it (L or LI) since it obviously is a monoacidic base containing two nitrogens.

CATALYTIC HYDROGENATION OF CYANAMIDES

n-Butyl-(4-diethylaminobutyl)cyanamide. When 107 g. (0.48 mole) of butyl-(4-diethylaminobutyl)cyanamide [b.p. 122–123° (0.4 mm.)] was shaken with 15 g. of Raney nickel in 200 ml. of absolute ethanol under an initial pressure of 1800 lb. of hydrogen, reduction began at 170°. After two hours approximately one mole of hydrogen had been absorbed.

Removal of the catalyst and ethanol and distillation of the residue yielded 39.0 g. of a colorless liquid b.p. 140–144° (26 mm.). Redistillation of this fraction over sodium gave 36.5 g. of a colorless liquid b.p. 137–138° (28 mm.); n_D^{25} 1.4410.

Anal. Calc'd for $C_{12}H_{28}N_2$: C, 72.1; H, 14.1.
Found: C, 71.9; H, 14.2.

A *dihydrobromide* prepared in ether and twice recrystallized from dioxane–ethanol mixture formed clusters of long, white needles m.p. 168–170° (softens 163–168°).

Anal. Calc'd for $C_{12}H_{30}Br_2N_2$: C, 39.8; H, 8.3; N, 7.7.
Found: C, 39.8; H, 8.6; N, 7.8.

These analytical data check for *1-n-butylamino-4-diethylaminobutane* and its *dihydrobromide*. The residue from the first distillation was fractionated. There was collected 50.0 g. of a colorless liquid b.p. 135–137° (1.4 mm.) which constitutes a recovery of 47% of the starting material.

Ethyl-β-bromoethylcyanamide. To 20.0 g. (0.11 mole) of ethyl-β-bromethylcyanamide (b.p. 92–94°/0.4 mm.) in 200 ml. of absolute methanol was added 20 g. of Raney nickel wet with ethanol. When placed in an Adams' shaker under 35 lbs. of hydrogen there took place, during five minutes' shaking, a pressure drop of 110% of that calculated for removal

of the bromine. Shaking for an additional ten minutes caused no further drop in pressure. After filtering off the catalyst, the methanol was removed by distillation at atmospheric pressure. Addition of 50 ml. of water to the residue caused the separation of no water-insoluble material. Extraction with ether (100 ml.) and removal of the ether from the extract left no residue. After making the aqueous solution strongly basic with potassium hydroxide, the mixture was warmed for twenty minutes on the steam-bath. After cooling, the oil was taken up in 100 ml. of ether and dried over potassium carbonate. Removal of the ether and distillation of the residue over sodium gave 7.2 g. (72%) of a colorless liquid of b.p. 126–129°. This material was readily soluble in water to give a strongly basic solution. Aspinall (40) reports b.p. 129–131° for N-ethylethylenediamine and gives the following derivatives: dipicrate m.p. 195°, dibenzamide m.p. 120°; di-(*p*-bromobenzenesulfonamide) m.p. 126°. When these derivatives were prepared from the above liquid, there were obtained the following: *dipicrate* m.p. 194–195°, *dibenzamide* 117–118°, *di-(p-bromobenzenesulfonamide)*, m.p. 124–125°. These data identify the above product as *N-ethylethylenediamine*. The residue from the distillation consisted of 2 to 3 g. of a brown, semi-solid material which was not investigated.

PREPARATION OF CYCLIC GUANIDINES

The *general procedure* for the preparation of these compounds was to mix equimolar quantities of the β-bromoethylcyanamide and the primary amine in absolute ethanol (50 ml. for 0.1 mole) and reflux three to four hours. The majority of the ethanol was removed by distillation and the solidified residue broken up and washed with ether and recrystallized.

1,3-Di-n-butyl-2-iminoimidazolidine hydrobromide was prepared in 86% yield from butyl-β-bromoethylcyanamide and *n*-butylamine. It formed white needles from dioxane–ethanol m.p. 177–179°.

Anal. Calc'd for $C_{11}H_{24}BrN_3$: C, 47.5; H, 8.7.
Found: C, 47.6; H, 8.7.

1-Ethyl-3-(2-hydroxyethyl)-2-iminoimidazolidine hydrobromide was prepared in 77% yield from ethyl-β-bromoethylcyanamide and ethanolamine. Colorless stout rods from butanol m.p. 122–123° were formed.

Anal. Calc'd for $C_7H_{16}BrN_3O$: C, 35.3; H, 6.8.
Found: C, 35.3; H, 7.0.

Bis-[2-(3-n-butyl-2-imino-1-imidazolidyl)ethyl]sulfide dihydrobromide was prepared in 95% yield from butyl-β-bromoethylcyanamide and β,β′-diaminodiethyl sulfide. It formed fine, white needles from isopropanol m.p. 204–206°.

Anal. Calc'd for $C_{18}H_{38}Br_2N_6S$: C, 40.8; H, 7.2.
Found: C, 40.5; H, 7.3.

Bis-[2-(3-n-butyl-2-imino-1-hexahydropyrimidyl)ethyl]sulfide dihydrobromide was prepared in 62% yield from butyl-γ-bromopropylcyanamide and β,β′-diaminodiethyl sulfide. It formed fine, white needles from isopropanol m.p. 198–199.5° (softens 196–198°).

Anal. Calc'd for $C_{20}H_{42}Br_2N_6S$: C, 43.0; H, 7.6.
Found: C, 42.7; H, 7.5.

Proof of structure of the guanidine (XXXIX). A solution of 48.0 g. of XXXIX (m.p. 177–179°) in 50 ml. of water was made alkaline. The resulting oily layer (slightly water soluble) was separated and refluxed eighteen hours with a solution of 40 g. of potassium hydroxide in 160 ml. of water. After cooling and dissolving the oil in ether, the ether solution was dried first with pellets of potassium hydroxide then over sodium. Removal of the ether and distillation of the residue over sodium gave 1.5 g. of a colorless forerun b.p. 80–123° (23 mm.), 4.9 g. (17%) of a colorless liquid (LX) b.p. 123–125° (23 mm.) and finally 19.2 g. of a colorless liquid b.p. 168–169° (23 mm.). A sample of this last fraction was converted to a *hydrobromide* in ether. After one recrystallization from dioxane–ethanol white needles of m.p. 177–179° were obtained. When mixed with a sample of XXXIX no depression in melting point was observed. This material b.p. 168–169° (23 mm.) is therefore the unhydrolyzed cyclic guanidine.

When a sample of the fraction b.p. 123–125° (23 mm.) in ether was treated with an ether solution of cyanogen bromide, there precipitated a white solid, which, after one recrystallization from dioxane–ethanol, formed white needles m.p. 177–179°. No melting point depression was observed when this was mixed with an original sample of XXXIX. The fraction 123–125° (23 mm.) must be *N,N'-di-n-butylethylenediamine*. King and McMillan (41) report b.p. 119–125° (23 mm.) for N,N'-di-*n*-butylethylenediamine. The formation of this hydrolysis product and its conversion back to XXXIX with cyanogen bromide furnish conclusive proof of the structure assigned to XXXIX.

SUMMARY

1. The reaction with cyanogen bromide of various N-alkylpyrrolidines and ethylenimines has been studied.
2. Two β-bromoethylalkylcyanamides have been prepared and shown to behave in an unpredicted manner upon catalytic reduction.
3. The reaction of a β-bromoethylalkylcyanamide with a primary amine has been shown to yield a cyclic guanidine.

NEW YORK 27, NEW YORK

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[CONTRIBUTION No. 177 FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, FORDHAM UNIVERSITY]

STUDIES IN THE THIOPHENE SERIES. V. WOLFF-KISHNER REDUCTIONS[1, 2]

WILLIAM J. KING[3] AND F. F. NORD

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The reduction of thienyl ketones to the corresponding alkyl thiophenes is usually carried out by means of the Clemmensen reduction (1). This method has the disadvantage, in many cases, of giving low yields, since excessive decomposition of the thiophene nucleus occurs. Although the yields can be improved by applying low temperatures, such a procedure proves time-consuming, sometimes requiring as much as fifty hours (2).

The Wolff-Kishner reaction has been utilized occasionally in the thiophene series, but without particular success. Steinkopf, *et al.* (3) prepared 2-ethylthiophene by first isolating the hydrazone of 2-acetylthiophene and then decomposing it by autoclaving for ten hours with sodium ethoxide. In this procedure they obtained an over-all yield of about 40%. Shepard (4) prepared 2-methyl-5-ethylthiophene in 40% yield by forming the semicarbazone of 2-methyl-5-acetylthiophene and heating it with potassium hydroxide. There appears to be no mention in the literature of the reduction of thiophene aldehydes to methylthiophenes. In view of the rather low yields obtained by the above methods and to avoid the application of autoclave equipment, it was decided to attempt the reduction at atmospheric pressure using ethylene glycol as a solvent (5).

It has now been found that various thiophene aldehydes and ketones can easily be reduced, without isolating the intermediate compound, *via* a simplified Wolff-Kishner reduction to give the corresponding alkyl compound in yields of 70–91%. The procedure consists essentially of mixing the carbonyl compound with an excess of 85% hydrazine hydrate in ethylene glycol solution and removing water and the remaining hydrazine hydrate by heating. The addition of potassium hydroxide and further heating leads to the formation of the reduced product. Unlike the benzene series, in which refluxing for at least three to four hours at temperatures above 170° is required, the hydrazones of the various thiophene compounds decompose vigorously between 90–140° and the reaction is usually completed in fifteen minutes. This method has been applied to nine thiophene aldehydes and two thiophene ketones. The collected data on the compounds prepared are summarized in Table I.

The acylation studies of Hartough and Kosak (11) offer ready access to thienyl ketones and it has been previously shown in this laboratory (12) that an aldehyde

[1] This investigation was aided by a grant from the Office of Naval Research. The analyses were carried out by Dr. F. Buhler of this Department.

[2] For Paper IV of this series see Crowe and Nord, *Nature*, **163**, May, (1949)

[3] Abridged from a part of the dissertation presented in partial fulfillment of the requirments for the degree of Doctor of Philosophy to the Graduate Faculty of Fordham University, 1949.

TABLE I

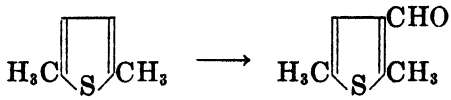
Alkyl Thiophenes Prepared via Wolff-Kishner Reduction

Carbonyl compound	Decomposition temp. (°C) of hydrazones	Product	Yield %	B.P., °C	n_D^{20}	Anal. Calc'd C%	Anal. Calc'd H%	Anal. Found C%	Anal. Found H%
Thiophene-2-aldehyde	90–100	2-Methylthiophene	78	112 –113[a]	1.5203[a]	61.07	6.16	60.85	6.10
2-Acetylthiophene	125–140	2-Ethylthiophene	91	133 –134.5[b]	1.5122	64.23	7.18	64.3	7.45
2-Propanoylthiophene	115–130	2-Propylthiophene	89	158 –159[c]	1.5050[c]	66.61	7.99	66.4	8.17
5-Methylthiophene-2-aldehyde	105–115	2,5-Dimethylthiophene	78	135 –136[d]	1.5132[d]	64.23	7.18	64.45	7.46
3-Methylthiophene-2-aldehyde	105–115	2,3-Dimethylthiophene	82	139.5–140.5[e]	1.5188[e]	64.23	7.18	64.4	7.35
5-Ethylthiophene-2-aldehyde	120–130	2-Methyl-5-ethylthiophene	81	159 –161[f]	1.5074[f]	66.61	7.99	66.95	8.19
5-Propylthiophene-2-aldehyde	115–125	2-Methyl-5-propylthiophene	83	179.5–180.5	1.5026	68.51	8.69	68.2	8.79
5-Chlorothiophene-2-aldehyde	100–120	2-Methyl-5-chlorothiophene	70	153.5–154.5[g]	1.5360[g]	45.25	3.80	45.28	4.01
2,5-Dimethylthiophene-3-aldehyde	120–130	2,3,5-Trimethylthiophene	74	163 –164[h]	1.5131[h]	66.61	7.99	66.4	8.00
2,3-Dimethylthiophene-5-aldehyde	115–130	2,3,5-Trimethylthiophene	80	163 –164[h]	1.5131[h]	66.61	7.99	66.5	8.10
2,3,5-Trimethylthiophene-4-aldehyde	120–130	2,3,4,5-Tetramethylthiophene	70	187 –189[i]	1.5196	68.51	8.69	68.2	8.48

[a] Ref. (6) gives b.p. 112.5°; n_D^{20} 1.5203.
[b] Ref. (3) gives b.p. 132–134°.
[c] Ref. (1d) gives b.p. 157–160°; n_D^{20} 1.5048.
[d] Ref. (7) gives b.p. 135.5–136°; n_D^{19} 1.51418.
[e] Ref. (4) gives b.p. 140.2–141.2°; n_D^{20} 1.5192.
[f] Ref. (4) gives b.p. 159.8–160.4; n_D^{20} 1.5073.
[g] Ref. (8) gives b.p. 153.7°; n_D^{17} 1.5367.
[h] Ref. (9) gives b.p. 163–165°/746 mm; n_D^{20} 1.5131.
[i] Ref. (10) gives b.p. 182–184°.

group can be introduced directly into thiophene and some substituted derivatives by means of the N-methylformanilide synthesis. Thus the facile reduction of these compounds offers a convenient way to obtain alkylated thiophenes. It, therefore, was deemed advisable to attempt the preparation of tetramethylthiophene to test the suitability of the reaction in both the α- and β-positions.

In forming thiophene aldehydes by means of the N-methylformanilide synthesis the entering aldehyde group ordinarily occupied any free α-position. If, however, both α-positions possess substituents, as in 2,5 dimethylthiophene, it is possible to obtain formylation in the β-position giving 2,5 dimethylthiophene-3-aldehyde (I).

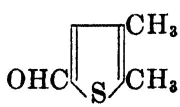


(I)

The aldehyde so obtained was oxidized to the corresponding acid and a mixed melting point with an authentic sample of 2,5-dimethyl-3-thiophenecarboxylic acid showed no depression, thus indicating that the aldehyde group had entered in the β-position. Reduction of I *via* the Wolff-Kishner method gave 2,3,5-trimethylthiophene and treatment of this with N-methylformanilide and phosphorus oxychloride gave 2,3,5-trimethylthiophene-4-aldehyde, which was again reduced to give 2,3,4,5-tetramethylthiophene.

It has also been found that 2,3-dimethylthiophene can be formylated to yield a dimethylthiophene aldehyde, which as expected proved to have the aldehyde group in the free α-position (II). This was shown by its conversion to the corresponding trimethylthiophene, which had the same physical constants as the 2,3,5-trimethylthiophene prepared from I. Furthermore, the N-methylformanilide synthesis when applied to the trimethylthiophene derived from II gave 2,3,5-trimethylthiophene-4-aldehyde, the semicarbazone of which showed no depression of its melting point, when mixed with an authentic sample. Therefore II is 2,3-dimethylthiophene-5-aldehyde.

(II)



Attempts to apply the N-methylformanilide synthesis to 2,5-dichlorothiophene were unsuccessful, probably due to the fact that the hydrogen atoms in the β-positions in this compound do not have the required mobility.

EXPERIMENTAL[4]

The procedure for the reduction of the carbonyl compounds was the same for all of the substances listed in Table I. As an example, the preparation of 2-methylthiophene is given.

[4] The thiophene used in these preparations was obtained through the courtesy of Drs. W. M. Holaday and G. A. Harrington of the Socony-Vacuum Oil Company.

2-Methylthiophene. Thiophene-2-aldehyde (28 g., 025 mole), 50 ml. of hydrazine hydrate (85%), and 200 cc. of ethylene glycol were placed in a 1-l. round-bottom flask fitted with a thermometer extending below the surface of the reaction mixture and arranged for distillation. The solution was heated to 130–160° and water and excess hydrazine distilled over. After thirty minutes a small amount of water-insoluble material was separated from the distillate and returned to the reaction flask. The solution was cooled below 60°, 50 g. of potassium hydroxide pellets was added, and an efficient reflux condenser was fitted to the flask. Heating was again applied with occasional shaking to bring the hydroxide into solution. A vigorous reaction with evolution of nitrogen occurred at 90–100°. After the reaction had subsided, the mixture was refluxed for fifteen minutes and then the methylthiophene was distilled from the reaction mixture. The distillate was extracted with ether, the ether extract washed with 6 *N* hydrochloric acid, dried over calcium chloride, the ether removed and the residual liquid fractionated over sodium. There was obtained 19.1 g. (78%) of 2-methylthiophene, b.p. 112–113°.

2,5-Dimethylthiophene-3-aldehyde. 2,5-Dimethylthiophene (56 g., 0.5 mole), 81.1 g. of N-methylformanilide (0.6 mole), and 92 g. of phosphorus oxychloride (0.6 mole) were placed in a flask fitted with a reflux condenser and the solution heated on a steam-bath until a vigorous evolution of hydrogen chloride gas commenced. Heating was removed until the reaction had subsided, then the flask was placed on a steam-bath for twenty minutes. At the end of this time cooling was applied and the contents of the flask carefully neutralized with aqueous sodium acetate. The mixture was then steam-distilled until no further oil came over. The distillate was extracted with ether, the ether extract washed with 6 *N* hydrochloric acid and with 5% sodium bicarbonate solution, dried over sodium sulfate and rectified. There was obtained 19.6 g. of 2,5-dimethylthiophene-3-aldehyde, b.p. 77–82°/4 mm.; n_D^{20} 1.5620. Fourteen grams of 2,5-dimethylthiophene were recovered in the fractionation. The yield of the aldehyde calculated on the basis of the utilized dimethylthiophene was 40%. The *semicarbazone* had m.p. 228–230°d.

Anal. Calc'd for $C_8H_{11}N_3OS$: N, 21.30. Found: N, 21.45.

The *acid* obtained by permanganate oxidation between 10–20° had m.p. 115–116°. A mixed m.p. with an authentic sample of 2,5-dimethylthiophene-3-carboxylic acid (13) showed no depression.

Anal. Calc'd for $C_7H_8O_2S$: C, 53.85; H, 5.15.
Found: C, 53.9; H, 5.15.

2,3-Dimethylthiophene-5-aldehyde. 2,3-Dimethylthiophene (33.6 g., 0.3 mole), 54 g. of N-methylformanilide (0.4 mole), and 61.3 g. of phosphorus oxychloride (0.4 mole) were placed in a round-bottom flask fitted with an efficient reflux condenser. The solution was allowed to heat up, until evolution of hydrogen chloride gas began. At this point, cooling was immediately applied by means of an ice-water bath. After the reaction had subsided, the flask was heated on the steam-bath for twenty minutes. Cooling was again applied and after careful neutralization with excess aqueous sodium acetate, the same isolation procedure as above was followed. There was obtained 35.4 g. (84.5%) of 2,3-dimethylthiophene-5-aldehyde, b.p. 80–85°/3 mm.; n_D^{20} 1.5770. The *semicarbazone* had m.p. 222–225°d.

Anal. Calc'd for $C_8H_{11}N_3OS$: N, 21.3. Found: N, 21.04.

2,3,5-Trimethylthiophene-4-aldehyde. 2,3,5-Trimethylthiophene (31.5 g., 0.25 mole), 67.6 g. of N-methylformanilide (0.5 mole), and 76.7 g. of phosphorus oxychloride (0.5 mole) were mixed in a flask fitted with a reflux condenser. The mixture was placed on a steam-bath until a vigorous evolution of hydrogen chloride gas began. Heating was removed until the reaction had subsided, and then was continued for twenty minutes. Following the same neutralization and isolation procedure as above, there was obtained upon rectification 15.8 g. of 2,3,5-trimethylthiophene-4-aldehyde, b.p. 87–91°/3mm., n_D^{20} 1.5553. During fractionation 8.5 g. of 2,3,5-trimethylthiophene was recovered. Therefore the yield of aldehyde on the basis of utilized methyl compound was 58%. The *semicarbazone* had a m.p. 179–180°.

Anal. Calc'd for $C_9H_{11}N_3OS$: N, 19.89. Found: N, 19.90.

SUMMARY

1. A modified Wolff-Kishner reduction has been applied to nine thiophene aldehydes and two thienyl ketones to give the corresponding alkylthiophenes in yields amounting to 70–91%.

2. The N-methylformanilide aldehyde synthesis has been utilized to prepare 2,3-dimethylthiophene-5-aldehyde, 2,5-dimethylthiophene-3-aldehyde, and 2,3,5-trimethylthiophene-4-aldehyde.

NEW YORK 58, N. Y.

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[Contribution from the Division of Chemistry, Research Department, Ciba Pharmaceutical Products, Inc.]

THE INTRODUCTION OF DOUBLE BONDS INTO STEROIDS BY THE USE OF THE HOFMANN DEGRADATION[1]

H. B. MACPHILLAMY and C. R. SCHOLZ

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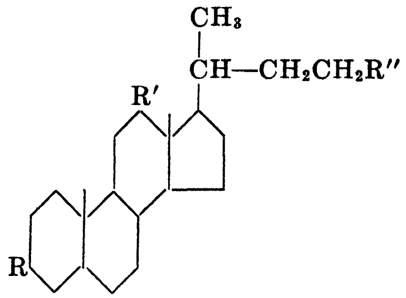
During the past few years various methods for the conversion of desoxycholic acid to compounds of the cortical hormone type have been investigated in these Laboratories. Some of the syntheses had steps which required the introduction of double bonds into the steroid molecule and it was thought that the Hofmann degradation (1) might be useful for this purpose.

Since a number of the important cortical hormones contain an oxygen function at C-11, the synthesis of such compounds is of considerable interest. One of the principal methods used for the introduction of this group starts with steroids containing a Δ^{11}-double bond, and therefore, we first applied the Hofmann degradation to the preparation of this type of unsaturation. 3(α)-Hydroxy-12-aminocholanic acid (I) was made by reducing the corresponding 12-oximino compound (II).[2] The amino acid thus obtained was esterified and the amino group methylated and quaternized to give ethyl 3(α)-hydroxycholanate 12-trimethylammonium iodide (III). After Hofmann degradation the reaction product, isolated as the acetate methyl ester, proved to be methyl 3(α)-acetoxy-Δ^{11}-cholenate (XIII). This series of reactions thus provides a new method for the introduction of the Δ^{11}-double bond.

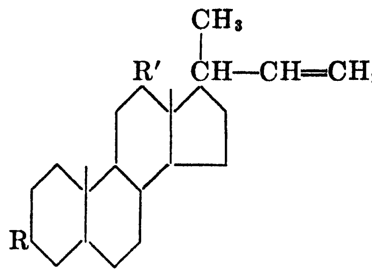
The Hofmann degradation was next investigated as a method for the preparation of Δ^{20}-pregnenes. Compounds of this type are important since they may be used as starting material for the synthesis of the ketol side chain characteristic of the cortical hormones. 3(α),12(α) - Diacetoxy - 20 - aminopregnane (XXIII) was prepared from 3(α),12(α)-diacetoxybisnorcholanic acid (XXII) through the Curtius reaction (2).[2] The amine was methylated and quaternized with methyl iodide and potassium carbonate to yield 3(α)-hydroxy-12(α)-acetoxypregnane 20-trimethylammonium iodide (XXIV), partial saponification having taken place during this reaction. When the Hofmann degradation was carried out with this compound the product, isolated as the diacetate, was shown to be 3(α),12(α)-diacetoxy-Δ^{20}-pregnene (XXV) by oxidation with chromium trioxide to the corresponding etiocholanic acid. After this work had been reported[1] Julian, Meyer, and Printy (3) published essentially the same synthesis of this compound using somewhat different reaction conditions.

[1] Presented in part before the Division of Medicinal Chemistry at the 112th Meeting of the American Chemical Society, New York City, September 17, 1947.

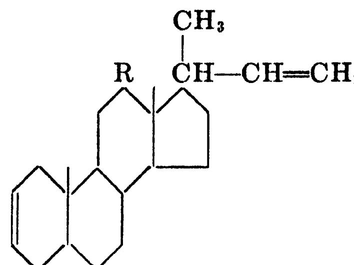
[2] Some of the amines described in this paper were first synthesized by Sarett [Merck Reports, Adrenal Cortical Problem, Committee on Medical Research of the Office of Research and Development] either by reduction of the oxime or by the Curtius method. They were further converted by means of nitrous acid [*cf.* reference (9)] to the corresponding unsaturated compounds which were identical with the corresponding products obtained in this work by means of the Hofmann degradation.



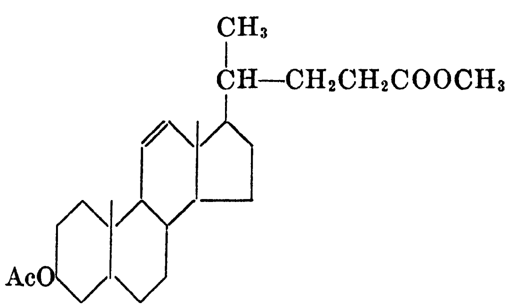
I R = OH, R′ = NH_2, R″ = COOH
II R = OH, R′ = NOH, R″ = COOH
III R = OH, R′ = $N(CH_3)_3I$, R″ = $COOC_2H_5$
IV R = OAc, R′ = OAc, R″ = NH_2
V R = OAc, R′ = OAc, R″ = COOH
VI R = OH, R′ = OAc, R″ = $N(CH_3)_3I$
VII R = H, R′ = OAc, R″ = $NH_2 \cdot HCl$
VIII R = H, R′ = OAc, R″ = COOH
IX R = H, R′ = OAc, R″ = $N(CH_3)_3I$
X R = OAc, R′ = H, R″ = NH_2
XI R = OAc, R′ = H, R″ = COOH
XII R = OAc, R′ = H, R″ = $N(CH_3)_3I$



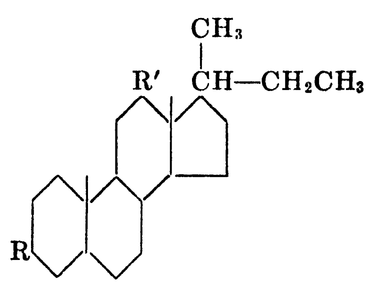
XIV R = OAc, R′ = OAc
XV R = H, R′ = OAc
XVI R = OAc, R′ = H



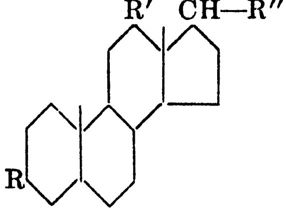
XVII R = OAc
XVIII R = H



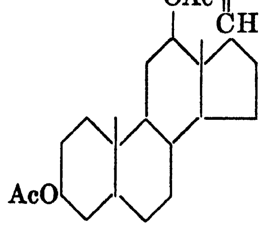
XIII



XIX R = H, R′ = OAc
XX R = H, R′ = H
XXI R = OAc, R′ = H



XXII R = OAc, R′ = OAc, R″ = COOH
XXIII R = OAc, R′ = OAc, R″ = NH_2
XXIV R = OH, R′ = OAc, R″ = $N(CH_3)_3I$



XXV

At the time this research began the long and cumbersome Barbier-Wieland procedure (4) was the only method available for the degradation of the bile acid side chain. In an attempt to find a better method 3(α),12(α)-diacetoxy-23-aminonorcholane (IV) was prepared from 3(α),12(α)-diacetoxycholanic acid (V) *via* the Curtius reaction. The amine was methylated and quaternized to give 3(α)-hydroxy-12(α)-acetoxynorcholane 23-trimethylammonium iodide (VI), which upon Hofmann degradation and acetylation of the product yielded 3(α),12(α)-diacetoxy-Δ^{22}-norcholene (XIV). Oxidation of this compound with chromium trioxide produced the bisnorcholanic acid XXII, which was identified as the methyl ester. Therefore, this series of reactions together with that described above provide a new approach to the side chain degradation. It cannot compare in yield, however, with the "N-bromosuccinimide method" of Meystre, Frey, Wettstein, and Miescher (5).

In addition to the norcholene XIV another product was isolated from the reaction mixture after the Hofmann degradation of the quaternary salt VI. Analytical data showed that this second compound had an additional double bond due to the loss of one of the hydroxyl groups during the reaction and consequently it must be either 3(α)-acetoxy-$\Delta^{11,22}$-norcholadiene or 12(α)-acetoxy-$\Delta^{2,22}$-norcholadiene (XVII).[3] To prove its structure both double bonds were catalytically hydrogenated and the completely reduced product was shown to be identical with 12(α)-acetoxynorcholane (XIX) and different from 3(α)-acetoxynorcholane (XXI). Therefore the second Hofmann degradation product was the diene XVII, the hydroxyl group at C-3 having been eliminated. The quaternary salt XII reacted in a similar manner yielding a small amount of the norcholadiene XVIII in addition to the main reaction product XVI. We encountered this side reaction only in the degradation of the 23-quaternary salts where the higher temperature necessary for their cleavage was responsible for the formation of the by-products.

EXPERIMENTAL[4]

INTRODUCTION OF THE Δ^{11}-DOUBLE BOND

Ethyl 3(α)-hydroxycholanate 12-trimethylammonium iodide (III). Ten grams of 3(α)-hydroxy-12-ketocholanic acid was refluxed for three hours in 80% aqueous alcohol with 1.1 moles of hydroxylamine hydrochloride and sodium acetate. On cooling and diluting with water the oxime crystallized. After recrystallization from methanol 10.1 g. (97%) of 3(α)-hydroxy-12-oximinocholanic acid (II) was obtained, m.p. 201–203°.[2]

Anal. Calc'd for $C_{24}H_{39}NO_4$: C, 71.07; H, 9.69; N, 3.45.

Found: C, 70.84; H, 9.69; N, 3.40.

The oxime II (7.0 g.) was reduced with 9.1 g. of sodium in 100 cc. of boiling isoamyl alcohol and yielded 3.0 g. (44%) of 3(α)-hydroxy-12-aminocholanic acid (I), m.p. 227–228°.[2] A 6.5-g. sample of the acid was esterified by refluxing it for three hours with 100 cc. of absolute ethanol containing 3 cc. of concentrated sulfuric acid. The alcoholic solution

[3] The second double bond has been placed in the Δ^2-position by analogy to the dehydration products of the bile acids, *cf.* Wieland, Kraus, Keller, and Ottawa, *Z. physiol. chem.*, **241**, 47 (1936).

[4] The microanalyses were carried out by Mr. Joseph Alicino, Metuchen, N. J. and Mr. George Stragand, Microchemical Laboratory, University of Pittsburgh, Pittsburgh, Pa. All melting points are corrected.

was concentrated, diluted with water, made alkaline with 10% sodium carbonate solution and the amino ester was extracted with ether. The extract was washed, dried, and the solvent removed leaving 6.7 g. of crude oily ethyl 3(α)-hydroxy-12-aminocholanate. This was not further purified but was used directly for the next step.

The quaternary salt was prepared by dissolving the above amino ester in 250 cc. of absolute ethanol and boiling the solution under reflux for forty-eight hours with the gradual addition of 50 cc. of methyl iodide and 50 g. of anhydrous potassium carbonate according to the directions of Woodward and Doering (6). At the end of this time the inorganic salts were filtered and the alcoholic solution concentrated to dryness *in vacuo*. The residue was taken up in chloroform, filtered, and the solvent was removed. The material remaining was dissolved in acetone and hexane was added. On standing, 1.5 g. of product crystallized, m.p. 158–160°; after solidification it remelted at 290°. The mother liquor fraction was re-methylated and quaternized and yielded 500 mg. of additional material raising the final yield of the quaternary salt III to 2.0 g. (22%).

Anal. Calc'd for $C_{29}H_{52}INO_3$: C, 59.21; H, 8.89; N, 2.38; I, 21.53.
Found: C, 59.20; H, 9.20; N, 2.30; I, 21.46.

Methyl 3(α)-acetoxy-Δ^{11}-cholenate (XIII). Two grams of quaternary salt III was subjected to the Hofmann degradation using essentially the same method as described by Woodward and Doering (6). The material was mixed with 3 cc. of water and 3 cc. of a solution of 5.0 g. of sodium hydroxide in 4 cc. of water was added. This strongly alkaline mixture was heated slowly to 160° in a Woods' metal bath. At that temperature trimethylamine could be detected and heating was continued for an additional half hour. Then the mixture was cooled, dissolved in water and the solution was acidified with concentrated hydrochloric acid. The steroid was extracted with ether and the extract was washed with water and then dried. On evaporation of the solvent 980 mg. of brown oil was obtained. This was esterified with diazomethane and acetylated with acetic anhydride in acetic acid solution using perchloric acid as a catalyst (7). The resulting 900 mg. of oily material was chromatographed in 50% benzene–hexane on 27 g. of acid-washed alumina. The fraction eluted with benzene yielded, after recrystallization from methanol, 200 mg. (35%) of crystalline product, m.p. 117–118° (reported 115–116°) (8).

INTRODUCTION OF THE Δ^{20}-DOUBLE BOND

3(α)-Hydroxy-12(α)-acetoxypregnane 20-trimethylammonium iodide (XXCIV). Twelve grams of 3(α),12(α)-diacetoxybisnorcholanic acid (XXII) was treated with 30 cc. of thionyl chloride at room temperature and the resulting acid chloride was reacted with 5 g. of sodium azide in dilute acetone solution as described by Sarett (9). After the steroid azide had been decomposed with dilute acetic acid the solution was made alkaline and the amine was extracted with ether. The ether solution was washed, dried and on treatment with hydrogen chloride gas 10.5 g. (97%) of amine (XXIII) hydrochloride precipitated.

Six grams of this hydrochloride was methylated and quaternized as previously described yielding 6.1 g. (83%) of crude quaternary salt. A 2.0-g. sample of this material was dissolved in water and the solution made alkaline to pH 10–11 with a 10% sodium hydroxide solution. Any incompletely methylated material was removed by extraction with ether. The remaining alkaline aqueous solution was neutralized with 10% hydrochloric acid and concentrated to dryness *in vacuo*. The residue was taken up in chloroform and filtered from the inorganic salts. On removal of the solvent 1.9 g. of material remained which yielded after recrystallization from an acetone–hexane mixture 1.6 g. of pure quaternary salt XXIV, m.p. 238–240°; after solidification it remelted at 285–290°. The presence of a small amount of water in the solvent used for crystallization was necessary since otherwise an amorphous precipitate was formed. The analytical data showed that saponification of one of the acetyl groups, presumably that at C-3, had taken place during the methylation step due to the alkalinity of the potassium carbonate used in this reaction.

Anal. Calc'd for $C_{26}H_{46}INO_3 \cdot H_2O$: C, 55.20; H, 8.50; I, 22.50.
Found: C, 55.23; H, 8.40; I, 22.80.

3(α),12(α)-Diacetoxy-Δ^{20}-pregnene (XXV) (3).[3] A suspension of 6.0 g. of the crude

quaternary salt XXIV in 10 cc. of 50% sodium hydroxide solution was subjected to the Hofmann degradation as previously described. Heating to 180° for a half hour was sufficient to complete the liberation of trimethylamine. After the mixture had cooled water was added and the steroid was extracted with ether. The extract was washed, dried and the solvent removed leaving 1.8 g. of oily material. This was acetylated and the resulting diacetate was recrystallized from methanol, m.p. 177–178°; yield 1.5 g. (35%).

Anal. Calc'd for $C_{25}H_{38}O_4$: C, 74.59, H, 9.51.

Found: C, 74.90; H, 9.25.

Methyl 3(α),12(α)-diacetoxyetiocholanate. A solution of 300 mg. of the pregnene XXV in 6 cc. of 90% glacial acetic acid was allowed to stand overnight at room temperature with 300 mg. of chromium trioxide. The reaction mixture was diluted with water, the excess chromium trioxide was destroyed with sodium bisulfite solution, the steroid was taken up in benzene, and the acid fraction was esterified with diazomethane and acetylated. The diacetate ester was chromatographed on acid-washed alumina yielding 170 mg. (52.5%) of material, m.p. 148–150° after recrystallization from methanol. A mixture with a known sample of methyl 3(α),12(α)-diacetoxyetiocholanate showed no m.p. depression.

INTRODUCTION OF THE Δ^{22}-DOUBLE BOND

3(α)-Hydroxy-12(α)-acetoxynorcholane 23-trimethylammonium iodide (VI) (10). Eighteen grams of 3(α),12(α)-diacetoxycholanic acid (V) was converted to the acid chloride. This was reacted with sodium azide and the azide subjected to the Curtius rearrangement as previously described yielding 14 g. (71.5%) of amorphous 3(α),12(α)-diacetoxy-23-amino-norcholane (IV) hydrochloride.[2]

Six grams of the hydrochloride was methylated and quaternized by the method already mentioned yielding 6.0 g. (82%) of crude material. This was purified and crystallized as described previously giving 4.8 g. of product, m.p. 227–228°.

Anal. Calc'd for $C_{28}H_{50}INO_3 \cdot H_2O$: C, 56.65; H, 8.83; I, 21.38.

Found: C, 56.83; H, 8.48; I, 21.36.

12(α)-Acetoxy-$\Delta^{2,22}$-norcholadiene (XVII) and 3(α),12(α)-diacetoxy-Δ^{22}-norcholene (XIV).[2] The Hofmann degradation was carried out with 13 g. of the crude quaternary salt VI. The material was divided into three portions and each was heated with 10 cc. of 50% sodium hydroxide solution to a temperature of 200–220°. This higher temperature was necessary to effect liberation of the trimethylamine in the case of the C-23-quaternary salts. When the decomposition was complete the batches were combined, diluted with water, and the steroid extracted with ether. After washing and drying the extract, the solvent was removed leaving 3.7 g. of oil. This was acetylated and chromatographed in hexane solution on 90 g. of acid-washed alumina. The fractions eluted with 10% and 20% benzene in hexane gave 650 mg. (8%) of crystals which melted at 143–145° after recrystallization from methanol and were identified as 12(α)-acetoxy-$\Delta^{2,22}$-norcholadiene (XVII).

Anal. Calc'd for $C_{25}H_{38}O_2$: C, 81.03; H, 10.33.

Found: C, 80.62; H, 10.20.

The fractions from the above chromatogram which were eluted with 5% to 25% ether in benzene yielded 1.3 g. (13.8%) of 3(α),12(α)-diacetoxy-Δ^{22}-norcholene (XIV), m.p. 133–134° after recrystallization from methanol.

Anal. Calc'd for $C_{27}H_{42}O_4$: C, 75.49; H, 9.76.

Found: C, 75.60; H, 9.82.

Methyl 3(α),12(α)-diacetoxybisnorcholanate. A 900-mg. sample of the norcholene XIV was oxidized in acetic acid solution with 900 mg. of chromium trioxide as described for the oxidation of the pregnene XXV. The product was similarly purified by esterification, acetylation, and chromatography yielding 470 mg. (49%) of material, m.p. 165–166° after recrystallization from ethanol. A mixture with a known sample of methyl 3(α),12(α)-diacetoxybisnorcholanate showed no m.p. depression.

12(α)-Acetoxynorcholane (XIX) from 12(α)-acetoxy-$\Delta^{2,22}$-norcholadiene (XVII). A suspension of 20 mg. of Adams' platinum oxide catalyst in 5 cc. of glacial acetic acid was pre-reduced and then 118 mg. of the diene XVII in 10 cc. of glacial acetic acid was added.

This mixture was hydrogenated at room temperature under slightly more than atmospheric pressure. About 2.3 moles of hydrogen were absorbed during one-half hour. The catalyst was filtered, the acetic acid removed *in vacuo* and the residue taken up in ether. The ether solution was washed with water and dilute sodium carbonate solution, dried and the solvent evaporated. The residue after recrystallization from methanol yielded 115 mg. (83.5%) of material, m.p. 83–84°.

Anal. Calc'd for $C_{25}H_{42}O_2$: C, 80.15; H, 11.30.

Found:[5] C, 79.74; H, 11.59.

12(α)-Acetoxy-23-aminonorcholane hydrochloride (VII). A 6.5-g. sample of 12(α)-acetoxycholanic acid (VIII) was converted to the acid chloride with thionyl chloride. This was reacted with sodium azide and the steroid azide decomposed with dilute acetic acid, yielding 4.5 g. of crude amine. An ether solution of the amine was treated with hydrogen chloride and 4.5 g. (68%) of amine hydrochloride was precipitated. It was recrystallized from methanol–ether and melted at 272–273°.

Anal. Calc'd for $C_{25}H_{44}ClNO_2$: C, 70.47; H, 10.17; Cl, 8.32.

Found: C, 70.24; H, 10.10; Cl, 8.56.

12(α)-Acetoxy-Δ^{22}-norcholene (XV). Three and one-half grams of the amine hydrochloride VII was methylated and quaternized, yielding 2.5 g. (52.5%) of tan crystalline quaternary salt IX, m.p. 232–240° (dec.). Two grams of this material was heated with 5 cc. of 50% sodium hydroxide solution to 220–230° for one-half hour. The reaction mixture was worked up as previously described and yielded 580 mg. of oily material. This was acetylated and chromatographed in hexane solution on 18 g. of acid-washed alumina. The fraction eluted with 25% benzene in hexane gave, after recrystallization from ethanol, 480 mg. (37%) of compound XV, m.p. 98–99°.

Anal. Calc'd for $C_{25}H_{40}O_2$: C, 80.59; H, 10.82.

Found: C, 81.03; H, 10.81.

12(α)-Acetoxynorcholane (XIX) from 12(α)-acetoxy-Δ^{22}-norcholene (XV). A solution of 120 mg. of the norcholene XV in acetic acid was hydrogenated with Adams' platinum oxide catalyst. About 1.2 moles of hydrogen were taken up and 115 mg. (96%) of product, m.p. 82–83°, was obtained. A mixture of this material with that obtained by the hydrogenation of the diene XVII showed no m.p. depression.

Anal. Calc'd for $C_{25}H_{42}O_2$: C, 80.15; H, 11.30.

Found: C, 79.97; H, 11.54.

3(α)-Acetoxy-23-aminonorcholane (X). When 4.0 g. of 3(α)-acetoxycholanic acid (XI) was converted to the acid chloride, then to the azide, and finally subjected to the Curtius rearrangement as previously described, a yield of 1.2 g. (31%) of the amine X was obtained. After recrystallization from methanol it melted at 121–122°. A somewhat better yield (40%) resulted when the modification of the Curtius reaction described by Hofmann and Bridgwater (11) was used.

Anal. Calc'd for $C_{25}H_{43}NO_2$: C, 77.06; H, 11.12; N, 3.59.

Found: C, 76.95; H, 11.15; N, 3.97.

3(α)-Acetoxynorcholane 23-trimethylammonium iodide (XII). Four grams of the amine X was methylated (3) by refluxing for four hours with 5 cc. of 90% formic acid and 3 cc. of 35% aqueous formaldehyde and the crude dimethylamine obtained by this reaction was quaternized (3) with methyl iodide in benzene solution. After recrystallization from acetone 2.4 g. (42%) of product, XII, m.p. 270–273° (dec.) was thus obtained.

Anal. Calc'd for $C_{28}H_{50}INO_2$: C, 60.09; H, 9.01; N, 2.50; I, 22.68.

Found: C, 60.80; H, 9.60; N, 3.00; I, 21.44.

These analytical results show that the material was impure but they are sufficient to serve as an indication of the compound's identity.

$\Delta^{2,22}$-Norcholadiene (XVIII) and 3(α)-acetoxy-Δ^{22}-norcholene (XVI). A 1.25-g. sample of the salt XII was treated with alkali as already described for the Hofmann degradation,

[5] Some of these low-melting compounds were difficult to burn so that repeated analyses were necessary to obtain check values.

heating to 230° being necessary to eliminate trimethylamine. About 350 mg. of oil was obtained and after acetylation it was chromatographed in hexane solution on 12 g. of acid-washed alumina. The fraction eluted with hexane gave 50 mg. (7.2%) of crystalline diene XVIII, m.p. 100–101.5°, after recrystallization from methanol.

Anal. Calc'd for $C_{23}H_{36}$: C, 88.39; H, 11.61.
Found: C, 88.45; H, 11.91.

The fractions of the above chromatogram which were eluted with 10% and 25% benzene in hexane yielded 60 mg. (7.5%) of the norcholene XVI, m.p. 94–95°, after recrystallization from methanol.

Anal. Calc'd for $C_{25}H_{40}O_2$: C, 80.59; H, 10.82.
Found: C, 80.52; H, 10.76.

Norcholane (XX). Twenty-eight milligrams of the diene XVIII was hydrogenated as previously described and 2.2 moles of hydrogen were absorbed. After recrystallization from methanol 20 mg. (71.5%) of material was obtained, m.p. 105–106° [reported 101–103° (12)].

Anal. Calc'd for $C_{23}H_{40}$: C, 87.26; H, 12.74.
Found: C, 87.56; H, 12.60.

3(α)-Acetoxynorcholane (XXI). Twenty-five milligrams of the norcholene XVI was similarly reduced taking up 1.1 moles of hydrogen. After recrystallization from methanol, 20 mg. (80%) of product was obtained, m.p. 82–83°. A mixture with the norcholane XIX, m.p. 82–83°, obtained by hydrogenating the diene XVII melted at 54–65°.

Anal. Calc'd for $C_{25}H_{42}O_2$: C, 80.15; H, 11.30.
Found: C, 79.87; H, 10.95.

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SUMMARY

1. The Hofmann degradation has been shown to provide a useful method for the introduction of double bonds into the steroid molecule.

2. It has been found that when the 3-hydroxy- and 3-acetoxy-23-quaternary salts of steroids are subjected to the Hofmann degradation, a small amount of material undergoes an additional reaction in which the substituent at C-3 is eliminated with the formation of a $\Delta^{2,22}$-diene.

SUMMIT, NEW JERSEY

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[Contribution from the Research Laboratories, School of Pharmacy, University of Maryland]

SYNTHESIS OF ISOQUINOLINE DERIVATIVES

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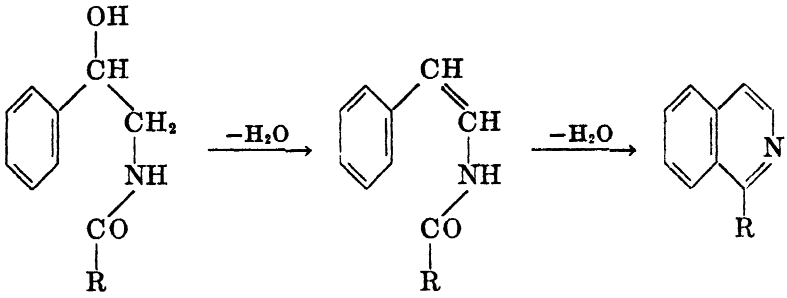
The readiness with which amines of type $ArCH_2CHRNH_2$ and alkanolamines of type $ArCHOHCHRNH_2$ may be prepared (1) and converted to their N-acyl derivatives makes them available for the preparation of isoquinolines of potential pharmacological interest.

Cyclodehydration of N-acyl-β-phenethylamines to 3,4-dihydroisoquinolines by the reaction of Bischler and Napieralski (2) consists in heating the amides with a dehydrating agent such as phosphorus pentoxide. An improvement attributable to Pictet (3) utilizes the temperature-moderating influence of a refluxing, inert solvent and is almost invariably employed. Direct formation of isoquinolines from acyl derivatives of β-hydroxy-β-phenethylamines, often called the Pictet-Gams (4) reaction, represents a loss of two molecules of water in a stepwise manner, as demonstrated by isolation of an intermediate styrylamide in some cases (5).



As would be expected, the presence of an electron-donating group *para* to the point of ring-closure greatly facilitates the reaction and usually minimizes any inhibiting influence which may exist. The present study was designed to explore the effects of substitution in the ethylamine side chain as well as to provide compounds for pharmacological evaluation; consequently it was desired that the isoquinoline derivatives prepared should be unsubstituted in the homocyclic ring. The isoquinolines prepared had hydrocarbon residues in the 1-, 3-, and 4-positions. No previous attempt had been made to evaluate the influence of such substitution upon the formation of the isoquinoline ring. Several 3,4-dihydroisoquinolines were prepared for comparison.[3]

In Table II are listed the bases prepared and the maximum yield of each

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[3] A study of the synthesis of 3,4-dihydroisoquinolines was made by Dey and Ramanathan (6); this paper was not abstracted and its contents were unknown before completion of the work reported here.

TABLE I

N-Acyl-β-phenylalkylamines

Name	Yield, %	M.P., °C.	Formula	Nitrogen, %	
				Calc'd	Found[a]
1-Phenyl-2-butyrylaminopropanol...........	79	93–94	$C_{13}H_{19}NO_2$	6.33	6.56
1-Phenyl-2-phenylacetylaminopropanol......	78	117–119	$C_{17}H_{19}NO_2$	5.20	5.27
1-Phenyl-2-benzoylamino-1-butanol.........	98	156–157	$C_{17}H_{19}NO_2$	5.20	5.39
2-Phenyl-3-benzoylamino-2-butanol.........	81	150–151	$C_{17}H_{19}NO_2$	5.20	5.40
1-Phenyl-2-benzoylamino-1-pentanol........	95	150–151	$C_{18}H_{21}NO_2$	4.94	5.10
1-Phenyl-2-benzoylamino-1-hexanol.........	74	151–152	$C_{19}H_{23}NO_2$	4.71	4.93
1-Phenyl-2-benzoylamino-1-octanol.........	86	77–78	$C_{21}H_{27}NO_2$	4.30	4.37
1-(α-Naphthyl)-2-benzoylaminopropanol.....	83	172–173	$C_{20}H_{19}NO_2$	4.59	4.73

[a] Microanalyses by Oakwold Laboratories, Alexandria, Va.

TABLE II

Substituted Isoquinolines

Cpd. No.	Substituents	Yield, %	Picrate M.P., °C.	Hydrochloride M.P., °C.	Formula	Nitrogen, %	
						Calc'd	Found[p]
1	1-Methyl-3,4-dihydro-	70	193[c]	196–198[j]	$C_{10}H_{12}ClN$	7.71	7.92
2	1-Phenyl-3,4-dihydro-	100	178[d]	245–248[k]	$C_{15}H_{14}ClN$	5.75	6.03
3	1-Benzyl-3,4-dihydro-	80[a]	176–178[e]	227–229	$C_{16}H_{16}ClN$	5.44	5.58
4	1-Phenyl-3-methyl-3,4-dihydro-	24	—[f]	205–210	$C_{16}H_{16}ClN$	5.44	5.61
5	1-Phenyl-4-methyl-3,4-dihydro-	92	152[g]	193	$C_{16}H_{16}ClN$	5.44	5.61
6	1-Phenyl-	91	174[h]	237–239[m]	$C_{15}H_{12}ClN$	5.80	5.59
7	1,3-Dimethyl-	37	—	168	$C_{11}H_{12}ClN$	7.23	7.06
8	1-Propyl-3-methyl-	35	—	165	$C_{13}H_{17}ClN$	—	—
9	1-Phenyl-3-methyl-	50[b]	188	229	$C_{16}H_{14}ClN$	5.48	5.26
10	1-Benzyl-3-methyl-	20	—	207(d)	$C_{17}H_{16}ClN$	5.19	5.32
11	1-Phenyl-3-ethyl-	26	—	210	$C_{17}H_{16}ClN$	5.19	5.13
12	1-Phenyl-4-ethyl-	10	165	113–115	$C_{17}H_{16}ClN$	5.19	5.48
13	1-Phenyl-3-propyl-	20	—	180–190	$C_{18}H_{18}ClN$	4.94	4.39[q]
14	1-Phenyl-3-butyl	1	—	*ca.* 130	$C_{19}H_{20}ClN$	—	—
15	1,3-Diphenyl-	20	185[i]	*ca.* 185[n]	$C_{21}H_{16}ClN$	4.41	4.32
16	1-Phenyl-3-methyl-5,6-benz-	12	—	235(d)	$C_{20}H_{16}ClN$	4.58	4.45

[a] The free base distilled at 130°/0.25 mm.; Ref. (12) gives b.p. 130–140°/35 mm.
[b] The free base melted at 123–125°.
[c] Ref. (3) gives m.p. 188–190°.
[d] Ref. (13) gives m.p. 175°.
[e] Ref. (12) gives m.p. 182°.
[f] Ref. (6) gives m.p. 150°.
[g] Ref. (6) gives m.p. 150°.
[h] Ref. (3) gives m.p. 164°.
[i] Ref. (14) gives m.p. 165°.
[j] Ref. (3) gives m.p. 160°.
[k] Ref. (3) gives m.p. 223°.
[m] Ref. (4) gives m.p. 236°.
[n] Ref. (14) gives m.p. 127°.
[p] Microanalyses by Oakwold Laboratories, Alexandria, Va.
[q] Not corroborative.

which could be obtained. It was found that in general isoquinolines may be prepared in as high yields as the corresponding 3,4-dihydroisoquinolines, though formation of the latter required less vigorous dehydrating conditions. In either series, compounds having aryl substituents in the 1-position were obtained in

TABLE III

CYCLODEHYDRATION DATA

CPD. NO.	AMIDE, (G.)	DEHYDRATING AGENT, (G.)	SOLVENT (ML.)	TIME, HRS.	YIELD, %
1	10	P_2O_5 (40)	Toluene (150)	0.5	11
1	5	P_2O_5 (10) + $POCl_3$ (10)	Xylene (75)	1	70
2	15	P_2O_5 (60)	Toluene (200)	3	83
2	3	Al_2O_3 (30)[a]	Decalin (100)	14	ca. 5[f]
2	3	P_2O_5 (10) + $POCl_3$ (10)	Xylene (25)	3	100
3	5	P_2O_5 (15)	Toluene (30)	1.5	24–60
3	5	$POCl_3$ (20)	Toluene (30)	1.5	0
3	5	P_2O_5 (20)	Xylene (100)	3.5	80
4	2	P_2O_5 (20)	Toluene (75)	3	12–19
4	5	P_2O_5 (25) + $POCl_3$ (50)	Xylene (150)	3	24
5	5	P_2O_5 (20)	Toluene (100)	3	92
6	2	P_2O_5 (20)	Toluene (75)	3	81
6	1	P_2O_5 (5) + $POCl_3$ (10)	Xylene (25)	3	91
7	2.7	P_2O_5 (15)	Toluene (50)	3	37
8	2	P_2O_5 (10) + $POCl_3$ (20)	Xylene (50)	3	35
9	2	P_2O_5 (20)	None[d]	1	8[f]
9	2	P_2O_5 (20)	Tetralin (75)[e]	1	35
9	2	P_2O_5 (20) + $POCl_3$ (20)	Xylene (50)	2.5	50
9	2	$POCl_3$ (40)	Xylene (50)	2.5	45[f]
10	2	P_2O_5 (4 × 5)[b]	Toluene (50)	2	10
10	2	P_2O_5 (20) + P_2O_5 (10)[c]	Tetralin (75)[e]	1	20
10	2	P_2O_5 (10) + $POCl_3$ (20)	Xylene (50)	3	16
11	2	P_2O_5 (10) + P_2O_5 (10)[b]	Toluene (50)	1.5	3.5
11	5	P_2O_5 (50) + $POCl_3$ (50)	Xylene (150)	3	26
12	5	P_2O_5 (50)	Xylene (150)	3	5–10
13	4	P_2O_5 (32)	Xylene (100)	3	3
13	2	P_2O_5 (20) + $POCl_3$ (20)	Xylene (50)	4	20
14	2.5	P_2O_5 (13) + $POCl_3$ (25)	Xylene (50)	3	1
15	2	P_2O_5 (16)	Xylene (75)	3	20
16	5	P_2O_5 (25) + $POCl_3$ (50)	Xylene (100)	3	12

[a] Activated by heating at 700°.
[b] Added at 30-min. intervals.
[c] Added after refluxing 15 minutes.
[d] At 250°.
[e] Practical grade tetralin reacted with P_2O_5. The material used was redistilled.
[f] Impure product.

higher yields than derivatives having 1-alkyl groups, in which cases there is evidence of considerable charring during dehydration. The use of phosphorus pentoxide in refluxing tetralin has been advocated for preparing 1-alkyl-3,4-dihydroisoquinolines (7).

Notably evident in Table II is the difficulty of cyclizing β-phenethylamines and β-hydroxy-β-phenethylamines having an alkyl group in the *alpha*-position, to the corresponding 3-alkyl derivatives. The adverse effect of an α-substituent is proportional to its size: 1-phenyl-3-butylisoquinoline was synthesized in only 1% yield and the 3-hexyl homolog could not be prepared. Isoquinolines with 3-phenyl substituents were more readily obtained than those with alkyl groups of comparable size.

1-Phenyl-4-methyl-3,4-dihydroisoquinoline was synthesized in excellent yield, indicating that a β-alkyl group does not hinder the cyclization of a β-phenethylamide. However, 1-phenyl-4-ethylisoquinoline could be prepared only in low yield and neither 1,4-diphenylisoquinoline nor 1-phenyl-3,4-dimethylisoquinoline could be prepared at all,[4] showing that a β-alkyl group definitely inhibits the cyclization of β-hydroxy-β-phenethylamides. It is known that the Pictet-Gams modification occasionally suffers from intervention of a side-reaction leading to an oxazoline (9), and such a transformation may have been responsible for the difficulties encountered. Attempts to prepare 1-phenyl-3-methyl-4-keto-3,4-dihydroisoquinoline were unsuccessful; previous attempts to synthesize such compounds resulted in the formation of oxazoles (10).

The conditions of cyclodehydration finally adopted for difficulty cyclized amides involve the use of both phosphorus pentoxide and phosphorus oxychloride in refluxing xylene. The choice is empirical, based upon numerous experiments as shown in Table III.

EXPERIMENTAL[5]

Amines. The β-phenethylamines used were available; the 1-phenyl-2-amino-1-alkanols were either available or were prepared according to an established procedure (1). Intermediates for the 4-alkylisoquinolines were obtained by the reaction of alkylmagnesium halides with the oximes of phenyl ketones under forcing conditions after the manner of Campbell and McKenna (11), but using dibutyl ether as solvent throughout the process.

Amides. The amides were prepared by treating each amine in alcohol-free ether with one equivalent each of 20% sodium hydroxide and the appropriate acid chloride, or by treating the amine hydrochloride in alcohol-free ether with two equivalents of 20% sodium hydroxide and one equivalent of acid chloride. The amides which were new compounds are described in Table I.

Isoquinoline derivatives. The substituted isoquinolines characterized in Table II were prepared by techniques outlined in Table III, which illustrates the effects upon yield of various conditions of reaction. Numerous experiments of little utility have been omitted from the table, including attempts to effect cyclization by means of concentrated sulfuric acid, boron trifluoride, phosphorus pentachloride, aluminum chloride, and heating *in vacuo*. As generally useful methods for cyclizing amides unactivated by alkoxyl groups, the following conditions are recommended:

3,4-Dihydroisoquinolines—the amide is refluxed with two parts each of phosphorus pentoxide and phosphorus oxychloride in fifteen parts of dry xylene for one hour under anhydrous conditions.

Isoquinolines—the amide is refluxed with five parts of phosphorus pentoxide and ten

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[4] The synthesis of 1,4-diphenylisoquinoline in 80% yield has been reported (8), but could not be confirmed.

[5] Melting points were determined with a calibrated apparatus.

parts of phosphorus oxychloride in twenty-five parts of dry xylene for three hours under anhydrous conditions.

At the end of the refluxing time the flask is cooled with ice-water while its contents are cautiously treated with ice to hydrolyze excess dehydrating agents. The layers are separated, the aqueous layer washed with benzene and then made strongly alkaline with 20% sodium hydroxide (a large volume of water is necessary to keep the inorganic salts in solution). The desired base is extracted with benzene, the extract dried over magnesium sulfate and treated with hydrogen chloride. An oily hydrochloride usually separates and may be crystallized from a mixture of isopropanol and ligroin after evaporation of the benzene, though crystallization is often induced with difficulty.

All of the *hydrochlorides* are colorless and moderately soluble in distilled water.

SUMMARY

A study is reported of the Pictet-Gams and the Bischler-Napieralski reactions as applied to the synthesis of isoquinolines and 3,4-dihydroisoquinolines alkylated in positions 3 and 4, but unsubstituted in the benzenoid ring.

Production of isoquinolines from N-acyl-β-hydroxy-β-phenethylamines required more drastic conditions but did not afford lower yields than the production of corresponding 3,4-dihydroisoquinolines. Synthesis of isoquinolines or 3,4-dihydroisoquinolines having alkyl groups in the 3-position was possible only in low yield, the yield decreasing with increase in size of the alkyl group. 3,4-Dihydroisoquinolines alkylated in the 4-position were prepared with greater facility than similar isoquinolines. In the 1- or 3-position a phenyl radical was less hindering than an alkyl group of comparable size.

Numerous preparative techniques were explored in seeking the most reliable methods.

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[CONTRIBUTION FROM THE TEXAS RESEARCH FOUNDATION]

ORGANIC COMPOUNDS OF TITANIUM. I. TETRAALKYL ORTHOTITANATES

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Several previous investigators (1–9) have reported the preparation of certain aliphatic esters of orthotitanic acid having the general formula $Ti(OR)_4$. Unlike the corresponding esters of orthosilicic acid, the alkyl silicates, these compounds are not formed by the direct action of titanium tetrachloride on the appropriate alcohol (5, 10). To date, the most generally satisfactory procedure [by Bischoff and Adkins (2) as modified by MacCorquodale and Adkins (3)] entails the reaction between the metal chloride and sodium alcoholate in alcohol solution:

$$TiCl_4 + 4NaOR\ (+xs.ROH) = Ti(OR)_4 + 4NaCl\ (+ROH)$$

This method, however, suffers from certain disadvantages and limitations. It necessitates the dissolution of metallic sodium in a large excess of alcohol prior to the addition of titanium tetrachloride. In the case of the primary alcohols, up to and including *n*-amyl alcohol, the reaction with sodium is reasonably fast and satisfactory; however, with secondary, tertiary, or higher molecular weight alcohols, it is exceedingly slow even at elevated temperatures. Further, in those instances where the alcohol is expensive or available only in small amounts, the need for a large excess is undesirable.

In this laboratory, the above procedure has been successfully employed; however, our results have indicated that, through certain minor modifications, it can be simplified and made more generally useful. In accord with the results of Havill, Joffe, and Post (10) on polyethers from trichlorosilane, benzene has been employed as a mutual solvent in this work and found to be very beneficial. Further, the order of addition of reagents has been changed. According to this modification, the titanium tetrachloride is allowed to react with an alcohol in benzene solution, and the sodium added later to this reaction mixture. Thus, both time and reagents are conserved while the yield and purity of products appear to be improved.

It has also been reported (6) that tetraalkyl orthotitanates can be prepared in good yield by the action of titanium tetrachloride on alcohols in the presence of ammonia or organic nitrogen bases. Repeated efforts in this laboratory to employ this method or to duplicate the examples cited in this patent have been uniformly unsuccessful. Only one experiment, designed to yield tetra-*tert*-butyl orthotitanate from *tert*-butanol in the presence of N,N-dimethylaniline, gave analytical evidence that some of the desired product was obtained. This could not be confirmed by isolation of a pure sample of the material in question. In substantiation of our negative results with this preparative method, it was found that anhydrous ammonia, in absolute alcohol, is capable of reacting with

tetraalkyl orthotitanates to form a white, insoluble, titanium-containing solid, from which the titanic ester cannot be regenerated. It should be noted, however, that several months after this experimental work was completed, information was received (11) which appeared to contradict these results. McTaggart and co-workers (12) have reported the preparation of butyl titanate from the condensation of *n*-butanol and titanium tetrachloride in the presence of gaseous ammonia. No analytical data or physical constants were reported. Work is now under way in this laboratory relative to the described process. While evidence is as yet incomplete, preliminary results would indicate that the butyl titanate described by these workers was probably a mixture consisting of tetra-*n*-butyl orthotitanate, chlorotri-*n*-butoxytitanium, and higher molecular weight condensed butyl titanate esters. None of the pure tetra-*n*-butyl orthotitanate has, so far, been obtained from this study. These results are in accord with our experience with *tert*-butanol referred to above.

Relatively few data are available with regard to the physical properties and constants of titanic esters. In our investigation the work of Bischoff and Adkins (2) has been extended to include additional physical characteristics as well as certain new compounds of this general class. It should be noted that the values reported for densities and refractive indices are merely the best approximations, since the tetraalkyl orthotitanates hydrolyze quite rapidly in moist air, and these values change slowly as the determinations are made.

Many experiments were conducted in an effort to prepare tetra-*tert*-butyl orthotitanate in the presence of condensing agents such as sodium, N,N-dimethylaniline, pyridine, ammonia, etc. None of the desired ester was obtained in this manner; *tert*-butyl chloride was usually the only volatile product which could be isolated. This new compound was finally secured through a transesterification between tetraethyl orthotitanate and an excess of *tert*-butanol.

A discussion of the preparation and properties of "tetramethyl orthotitanate" has been avoided since this material appears to warrant a detailed and separate report at a later date.

EXPERIMENTAL

Tetraalkyl orthotitanates which have been prepared in this investigation include the ethyl, *n*-propyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, and *n*-octyl esters. Of these, the ethyl and *n*-butyl compounds have been reported previously, but it appears that the *n*-propyl, isobutyl, *sec*-butyl, *tert*-butyl, and *n*-octyl derivatives have been prepared for the first time in this study. The first four examples could be made by the original method (2) discussed above, whereas the *sec*-butyl and *n*-octyl esters could be made successfully only by the new technique. As mentioned before, the *tert*-butyl analog could not be obtained by either method, and was secured only through an ester exchange reaction. With this exception, the general synthetic method was identical for all members of this series of compounds, hence a description of the experimental work with secondary butanol will suffice as an example:

Tetra-sec-butyl orthotitanate, $Ti(O\text{-}s\text{-}C_4H_9)_4$. A solution of 296.5 grams (4.0 moles) of freshly distilled *sec*-butanol in 300 ml. of anhydrous benzene was placed in a two-liter, 3-neck flask equipped with a dropping-funnel, reflux condenser with calcium chloride drying tube, thermometer, and a mercury-seal mechanical agitator. External cooling lowered the temperature of this mixture to 0–10°. Ninety-five grams (95.0 g., 0.5 mole) of Fisher C.P.

titanium tetrachloride was added dropwise over a period of about 80 minutes while the temperature was maintained below 10°. After 45 minutes further agitation at this temperature, the reaction mixture was allowed to warm slowly to room temperature (*ca.* 30°) and stirred for two hours longer. Then metallic sodium (46.0 grams, 2.0 moles) was added in small pieces at such a rate that the temperature rose slowly to 75°. After standing overnight at 30° the reaction mixture was heated to reflux for 3 hours. A further portion of benzene (100 ml.) was added during this period to reduce the gel-like consistency and facilitate agitation. The reaction product was cooled somewhat and centrifuged to remove sodium chloride. The solid residue was washed twice with hot benzene (100 ml.) and the centrifugate added to the initial benzene solution.

Atmospheric distillation of the solvent served to concentrate the product, which was isolated by vacuum fractionation, b.p. 90–110°/1–3 mm. The crude, water-white oil weighed 71.5 grams (0.2 mole); yield 40%. After careful fractionation through a 24-inch Widmer column, the product showed the following properties: b.p. 90–92°/0.5–1.0 mm.; n_D^{25} 1.4550 (Abbé); d_4^{25} 0.9196; viscous, water-white oil having an odor of freshly cut apples. The recovery of purified product amounted to approximately 90% of the crude material described above.

This titanic acid ester hydrolyzes quite readily when exposed to moist air with the deposition of hydrated orthotitanic acid. This fact was utilized to design a very simple analytical method, which is described below.

Anal. Calc'd for $Ti(OC_4H_9)_4$:TiO_2, 23.48. Found: TiO_2, 23.24.

The qualitative solubilities of this compound, tetra-*sec*-butyl orthotitanate, are exemplary of the general class of orthotitanic esters (See Table I).

Attempted preparation of tetraalkyl orthotitanates using basic nitrogen condensing agents. In an effort to employ ammonia and organic nitrogen bases as condensing agents as reported previously (6), a large number of experiments were conducted. Pyridine, N,N-dimethylaniline, and ammonia have been studied in connection with ethanol, *n*-propanol, isopropanol, *n*-butanol, *tert*-butanol, and *n*-octanol with and without solvents. With the exception of the single result mentioned above (with *tert*-butanol), the results were uniformly negative. A description of the use of N,N-dimethylaniline will serve as an example of these experiments. In an apparatus similar to that described above, 92.1 grams (2.0 moles) of absolute ethanol was dissolved in 250 ml. of anhydrous benzene and chilled to 0–10°. With vigorous agitation, 47.5 grams (0.25 mole) of titanium tetrachloride was dropped in during 45 minutes. After 30 minutes at the above temperature, the mixture was allowed to warm slowly to room temperature and stirred for an additional 30 minutes. External cooling served to reduce the temperature again to 0–10°, and a solution of 145.5 grams (1.2 mole) of anhydrous N,N-dimethylaniline in 150 ml. of dry benzene was added during 30 minutes. This mixture was stirred for ½ hour at 10°, warmed to room temperature for 4 hours, and finally heated to reflux for 1 hour.

Atmospheric distillation of solvent served to concentrate the reaction products which were subsequently isolated by fractionation at 3–4 mm. After a considerable fore-run of low-boiling material (below 100°), 21.7 grams of viscous yellow oil was collected, b.p. 100–160°/10 mm. Extensive decomposition occurred during this distillation, such that a lower operating pressure could not be obtained. This crude product, which partially solidified on cooling, was redistilled through a 24-inch Widmer column. The fore-run consisted of dimethylaniline, but a very small amount of water-white oil was collected at 75–78°/1 mm. On cooling, this material solidified, m.p. 75–6°. This purified product, however, contained no titanium and, obviously, was not the expected ester. None of the desired tetraethyl orthotitanate could be isolated from this reaction.

Tetra-tert-butyl orthotitanate, $Ti(O\text{-}t\text{-}C_4H_9)_4$. Seventy-four grams (74.0 g., 1.0 mole) of *tert*-butanol was mixed with 22.8 grams (0.1 mole) of crude tetraethyl orthotitanate and warmed to rapid reflux. Volatile material was allowed to distil slowly until the pot temperature reached 100°. A fresh portion of 37.0 grams (0.5 mole) of *tert*-butanol was added and the slow distillation repeated. Finally, yet a third portion of fresh *tert*-butanol (37.0 g.,

0.5 mole) was added and the process repeated. Distillation of the final residue at reduced pressure yielded 15.2 grams (0.045 mole, 45%) of the desired product, tetra-*tert*-butyl orthotitanate, boiling at 62–3°/1 mm.; n_D^{20} 1.4436; d_4^{20} 0.8893.

Anal. Calc'd for $Ti(OC_4H_9)_4$:TiO_2, 23.48. Found: TiO_2, 23.36.

Analytical Method. A simple but effective analytical procedure was devised to determine the titanium content of these products. It involved weighing a sample (*ca.* 0.25 g.) of the

TABLE I

SOLUBILITIES OF TETRAALKYL ORTHOTITANATES

SOLVENT	COLD	HOT
Water	Insol. white ppt.	Insol. white ppt.
Ethanol	Soluble	Soluble
n-Butanol	Soluble	Soluble
Benzene	Soluble	Soluble
Chloroform	Soluble	Soluble
2,3-Dimethylbutane	Soluble	Soluble
Diethyl ether	Soluble	Soluble
Carbon disulfide	Soluble	Soluble
Acetone	Insol. white ppt.	Insol. white ppt.
Octanone-2	Sol., yellow color	Insol. yellow ppt.
Ethyl acetate	Insol. white ppt.	Soluble
Acetic acid	Insol. white ppt.	Insol. white ppt.
Pyridine	Soluble	White, gel-like solid
Turpentine	Soluble	Soluble, yellow color
Linseed Oil	Soluble	Soluble, red color, viscous
Soybean Oil	Soluble	Soluble, ruby red color, viscous
Glycerine	Soluble, viscous	Soluble, white opalescence, viscous

TABLE II

TETRAALKYL ORTHOTITANATES, $Ti(OR)_4$

R	YIELD, %	B.P., MM.	n^t_D	d^t_4
C_2H_5	66.0	104°/1	1.5051/35°	1.107/35°
n-C_3H_7	42.0	170°/3	1.4803/35°	0.9970/35°
n-C_4H_9	49.7	134–136°/0.5–1	1.4863/35°	.9927/35°
iso-C_4H_9	68.8	141°/1	1.4749/54°	.9750/55°
sec-C_4H_9	40.0	90–92°/0.5–1	1.4550/35°	.9196/35°
tert-C_4H_9	45.0	62–63°/1	1.4436/20°	.8893/20°
n-C_8H_{17}	63.3	219°/1	1.4762/35°	—

ester directly into an ignited and weighed crucible. The sample was covered with 10 ml. of distilled water containing 2 drops of concentrated nitric acid. The crucible was then heated on a hot plate until almost all of the water had evaporated. It was then cooled, and a fresh portion of 10 ml. of water and 2 ml. of concentrated nitric acid added. Careful evaporation (considerably facilitated by an electric heat lamp suspended above the crucible) was followed by ignition for one hour at 600–650°. The residue was weighed as titanium dioxide. In this laboratory, duplicate analyses have usually agreed within 1 part in 300.

DISCUSSION

A summary of data relative to yields and physical constants appears in Table II. In general terms, the tetraalkyl orthotitanates may be described as high-boiling, clear, viscous oils; they vary in color from water-white to a light yellow depending upon the care with which purification is accomplished. They tend to become extremely viscous at room temperature, and in the case of the isobutyl ester, a low-melting solid is formed. These products have a mild, fruit-like odor.

It has been the general experience in this laboratory, that the yields of tetraalkyl orthotitanates claimed by Adkins and co-workers (2, 3) could not be achieved. Whereas their method usually yielded 25–35% of the desired product (claimed 67–81%), the modified method described above gave 45–65%. In addition, the latter method appeared to give a purer product (judging from color, analysis, and physical constants). Furthermore, the original method failed when applied to *n*-octanol and *sec*-butanol while the modified process worked reasonably satisfactorily.

SUMMARY

An improved method for the preparation of tetraalkyl orthotitanates is described together with the physical constants of several new examples of this type of ester. Those compounds which have been prepared for the first time are: tetra-*n*-propyl orthotitanate, tetraisobutyl orthotitanate, tetra-*sec*-butyl orthotitanate, tetra-*tert*-butyl orthotitanate, and tetra-*n*-octyl orthotitanate.

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[Contribution from the Division of Chemistry, Research Department, Ciba Pharmaceutical Products, Inc.]

THE WOHL-ZIEGLER BROMINATION OF ENOL ACETATES OF 20-KETO STEROIDS

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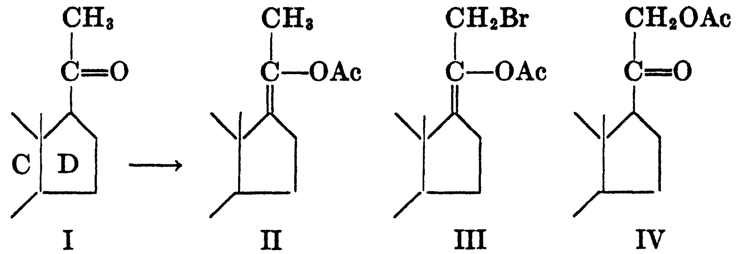
The reaction of N-bromosuccinimide (Wohl-Ziegler reaction) with enol esters or ethers does not seem to have been studied as yet (1). Recently, Gallagher

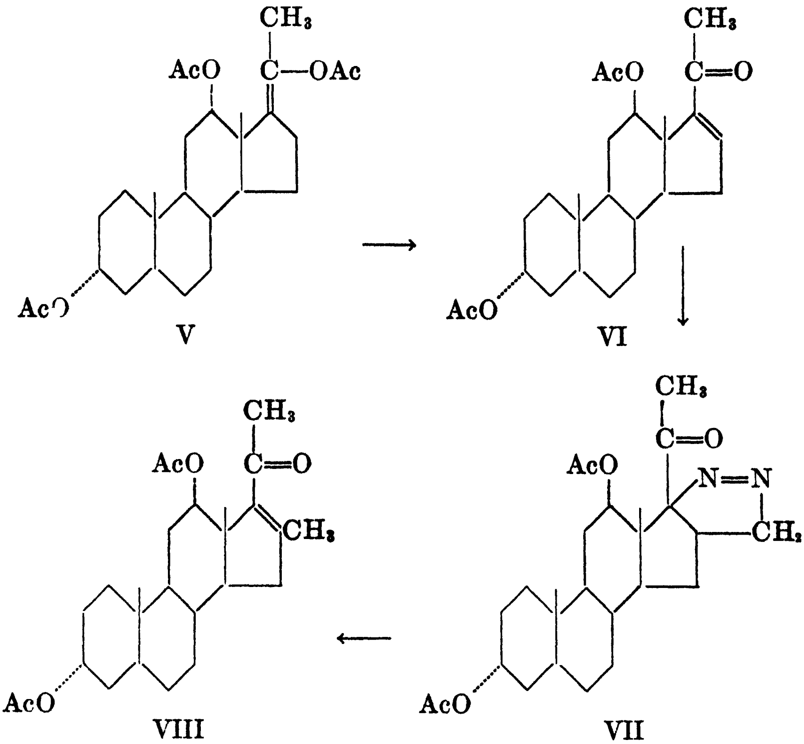


and co-workers (2) described a satisfactory method for the conversion of 20-keto steroids (I) into their enol acetates (II) by refluxing with acetic anhydride and *p*-toluenesulfonic acid. It was of interest to investigate the action of N-bromosuccinimide (NBS) on such enol acetates (II), since if a 21-bromo derivative (III) were formed, acetolysis followed by cleavage of the enol acetate grouping would afford a new method for converting 20-keto pregnane derivatives (I) into members of the cortical hormone series (IV).

Initial bromination experiments were carried out with the readily available, crystalline Δ^{17}-3(α),12(α),20-triacetoxypregnene (V) in the presence of peroxide; after removal of succinimide and solvent, the residue was refluxed with potassium acetate in acetone solution to effect substitution with any reactive bromide. The crystalline product thus obtained contained by analysis only two acetoxyl groups and exhibited a pronounced maximum at 238 mμ. On that basis, it seemed almost certain that the substance was the previously unknown Δ^{16}-3(α),12(α)-diacetoxy-20-ketopregnene (VI). Its structure was confirmed further when it was noted that the compound underwent the Azzarello reaction (3) with diazomethane to afford a pyrazoline (VII), a behavior characteristic of Δ^{16}-20-keto steroids (4). Finally, in agreement with related pyrazolines (4), VII readily lost the elements of nitrogen on sublimation to lead to a new unsaturated ketone. According to Wettstein (4), the most probable structure for the product of such a thermal treatment is that of a Δ^{16}-16-methyl-20-ketone (VIII).[1]

Further investigation of this unexpected reaction between NBS and the enol acetate (V) indicated that the treatment with acetate could be omitted and that

[1] Ring enlargement to a Δ^{17}-D-homo-20-ketone is not excluded, but the observed ultraviolet absorption maximum at 248 mμ is in good agreement with that predicted (247 mμ) on the basis of Woodward's rule [*J. Am. Chem. Soc.*, **64**, 76 (1942)] for the ketone (VIII) (the possible effect of the five-membered ring is not considered in this calculation).



after refluxing for five minutes with NBS, followed by filtration, removal of carbon tetrachloride, and direct crystallization, 45–50% of the unsaturated ketone (VI) could be isolated. Increasing the reflux time to one-half hour did not raise the yield and the absence of light and peroxide had no deleterious effect. This rapid rate of reaction of the enol acetates (II) with NBS is in marked contrast to the behavior of the corresponding 20-keto steroids (I) (5).

The Wohl-Ziegler reaction was next applied to the crude 20-enol acetate of 3(β)-acetoxy-20-keto*allo*pregnane, which appears to consist of a mixture of *cis* and *trans* isomers (2), and led to the known (6, 7) Δ^{16}-3(β)-acetoxy-20-keto*allo*-pregnene in 25% over-all yield (based on *allo*pregnanolone acetate). Recently (8), Δ^{16}-20-keto steroids have gained increased importance as starting materials for the preparation of 17(α)-hydroxypregnanes, and a new synthesis of such unsaturated ketones is clearly desirable. While in certain instances (6, 7) the conventional procedure (involving bromination of the 20-ketone followed by dehydrobromination with pyridine) is satisfactory, it fails in other cases such as the 3(α),12(α)-diacetoxy-20-ketopregnane where bromination results in difficultly separable mixtures (9). The present investigation demonstrates that the Wohl-Ziegler reaction *via* the enol acetates represents a satisfactory alternative.

The mechanism of the reaction of NBS with enolic derivatives of 20-keto steroids is not quite clear, but assuming a free radical mechanism for allylic brominations with NBS (1), initial attack at C_{16} followed by a shift of the double

bond (*i.e.* the single electron) would afford a reasonable path for the direct production of VI and acetyl bromide.

EXPERIMENTAL[1]

The Wohl-Ziegler reaction on Δ^{17}-3(α),12(α),20-triacetoxypregnene (*V*). A solution of 230 mg. of the enol acetate (V), prepared according to Gallagher (2), in 8 cc. of dry carbon tetrachloride was refluxed with 90 mg. of N-bromosuccinimide from five to thirty minutes. All of the reagent was consumed within four minutes and the colorless solution evolved considerable amounts of fumes (acetyl bromide and/or hydrogen bromide). The succinimide was removed by filtration and the filtrate was distilled to dryness under reduced pressure. Trituration of the residue with hexane afforded 100 mg. (48%) of colorless solid melting at 180–185°. The analytical sample of the unsaturated ketone (VI) crystallized from a mixture of hexane and acetone as colorless needles with m.p. 193–193.5°, $[\alpha]_D^{28}$ +113°, maxima at 238 mμ (log E 4.07) and 315 mμ (log E 2.02) and minimum at 281 mμ (log E 1.81).

Anal. Calc'd for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71; acetyl, 20.67.

Found: C, 71.71; H, 8.37; acetyl, 20.53.

The *pyrazoline derivative* (VII) was prepared according to Wettstein's method (4) by allowing an ethereal solution of 255 mg. of the Δ^{16}-20-ketone (VI) to stand with an excess of diazomethane for twenty hours. Evaporation in a current of air and recrystallization from hexane–acetone gave 220 mg. (79%) of colorless needles with m.p. 175–176° (gas; on cooling and remelting, a melting point of 207–210° was observed), $[\alpha]_D^{28}$ +142°.

Anal. Calc'd for $C_{26}H_{38}N_2O_5$: C, 68.09; H, 8.35; N, 6.11.

Found: C, 67.82; H, 8.24; N, 6.59.

Fifty milligrams of the pyrazoline (VII) was sublimed at 170° and 0.002 mm., and the sublimate was recrystallized from hexane–acetone affording 40 mg. (85%) of the *Δ^{16}-16-methyl-20-ketone* (VIII) with m.p. 213–214°, $[\alpha]_D^{23}$ +128°, maximum at 248 mμ (log E 4.00).

Anal. Calc'd for $C_{26}H_{38}O_5$: C, 72.53; H, 8.90.

Found: C, 72.23; H, 8.49.

The Wohl-Ziegler reaction on Δ^{17}-3(β),20-diacetoxyallopregnene. Δ^5-Pregnenolone acetate was hydrogenated completely in acetic acid solution with platinum oxide catalyst and the product was oxidized with chromic anhydride in the same solvent. The resulting 3(β)-acetoxy-20-keto*allo*pregnane (1.4 g.) was converted to the enol acetate (2), and the colored impurities were removed by passage through a short column of alumina. The colorless, oily enol acetate (1.55 g.) thus obtained was refluxed with 0.7 g. of N-bromosuccinimide and 15 mg. of benzoyl peroxide in 40 cc. of carbon tetrachloride for seven minutes. The usual work-up including chromatography gave 0.35 g. (25% over-all yield based on 20-ketone) of Δ^{16}-3(β)-acetoxy-20-keto*allo*pregnene with m.p. 154–157°, which according to Plattner, *et al.* (6), represents satisfactory material for subsequent reactions. Several recrystallizations from hexane gave colorless crystals with m.p. 161–163°, $[\alpha]_D^{28}$ +43.6°, maxima at 240 mμ (log E 4.01) and 310 mμ (log E 2.70) and minimum at 275 mμ (log E 2.32); reported: m.p. 163–165° (7), 166–167° (vac.) (6), $[\alpha]_D$ +42.2° (6).[3]

Anal. Calc'd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56.

Found: C, 77.30; H, 9.56.

Acknowledgment. Grateful acknowledgment is made to the Misses Frances Hoffman and Edwina Leathem for technical assistance and to Dr. Paul Ulshafer for a supply of 3,12-diacetoxy-20-ketopregnane.

[1] Melting points are corrected. All rotations were determined in a 0.5% chloroform solution and absorption spectra in 95% ethanol. The microanalyses were performed by Mr. Joseph F. Alicino, Metuchen, N. J.

[3] KLYNE, *et al.*, (10) obtained the following constants on a sample supplied by Plattner (6): m.p. 165–167°, $[\alpha]_D^{20}$ +36.3° ± 7°, maxima at 240 mμ (log E 3.93) and 320 mμ (log E 1.92) in ethanol.

SUMMARY

As demonstrated by the two examples, enol acetates of 20-keto steroids react rapidly with N-bromosuccinimide with formation of the corresponding Δ^{16}-20-keto steroids in one step.

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THE SYNTHESIS OF CUSCOHYGRINE

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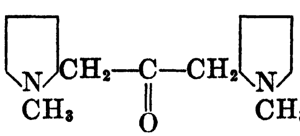
Two structures, I and II, have been proposed for cuscohygrine, one of the minor alkaloids of South American coca leaves. Formula I, advanced by Liebermann in a note to Willstätter (1), appears to best explain the isolation of hendecane and 6-hendecanol from Hofmann degradation of dihydrocuscohygrine; however, a rearrangement of the dihydro compound corresponding to structure II during the degradation has also been suggested to explain the appearance of these products (2).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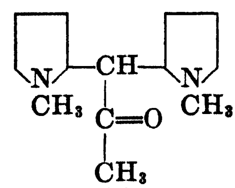

II

The objective of the present investigation was to establish the structure of cuscohygrine by an unequivocal synthesis of 1,3-bis(1′-methyl-2′-pyrrolidyl)-2-propanone (I). At the same time, it was hoped to obtain information on the relative configuration of the two similar asymmetric carbon atoms in this structure. Natural cuscohygrine is optically inactive, could not be resolved into active components (3), and on reduction gave two alcohols (2). These facts are consistent with a *meso* configuration for the natural material but this assumption does not explain the existence of two isomeric hydrazones (4). The suggestion of Sohl and Shriner (5), that the natural material is a mixture of *meso* and racemic forms, would account for the two hydrazones but should lead to three rather than two alcohols.

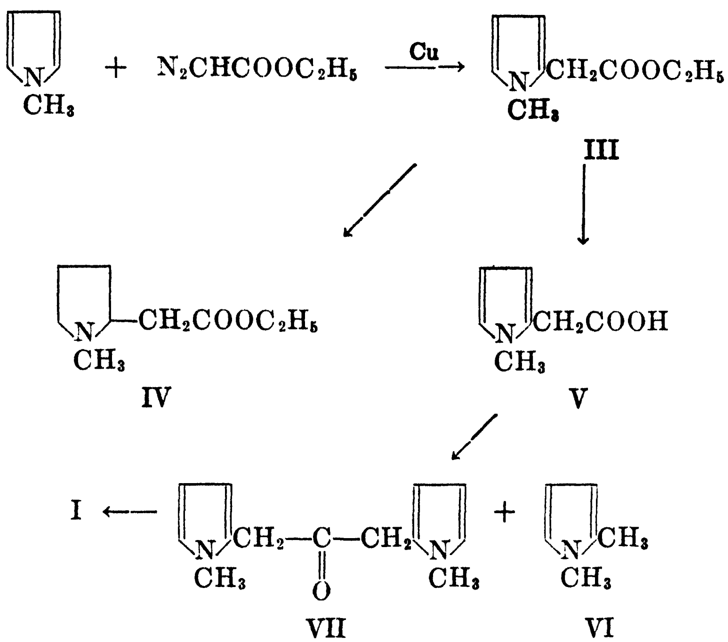
Two syntheses of cuscohygrine have been reported in the recent literature.[1] The first, by Lazurevskii (6), was purportedly accomplished by pyrolysis of the barium salt of 1-methyl-2-pyrrolidineacetic acid; however, no experimental details were given. A successful synthesis by this method seemed surprising since the compound being pyrolyzed was a substituted β-amino acid and might be expected to suffer cleavage of the amino group under the drastic conditions required. In view of this, an attempt was made to repeat the synthesis. Ethyl 1-methyl-2-pyrrolidineacetate (IV), prepared in good yield as outlined below by several modifications of the procedure of Sohl and Shriner (5), was converted to

[1] After this paper had been accepted for publication, a note appeared by Anet, Hughes, and Ritchie, *Nature*, 163, 289 (1949), in which the synthesis of cuscohygrine was reported from acetone dicarboxylic acid and γ-methylaminobutyraldehyde. However, no experimental details were presented.

the barium salt and the latter dry-distilled. The pyrolysate was then fractionally distilled and four fractions were obtained, all of which appeared to be unsaturated, secondary amines. No evidence could be obtained for the presence of cuscohygrine in any of the various fractions.

The second reported synthesis, by Späth and Tuppy (7), became known to us only after our work had been practically completed. They describe a successful synthesis of cuscohygrine by substantially the same method used in the present work. However, there appear to be sufficient differences, especially in the characterization of the final product, to warrant reporting our results at this time. No mention is made by Späth and Tuppy of the prior claim to synthesis by Lazurevskii, undoubtedly because this information was unavailable to them.

In the present synthesis, 1,3-bis(1′-methyl-2′-pyrryl)-2-propanone (VII) was prepared by pyrolysis of the barium salt of 1-methyl-2-pyrroleacetic acid (V), and the resulting ketone was catalytically hydrogenated to give the final product. When purifying the crude acid (V), obtained by saponification of the ester (III), it was found that a surprisingly facile decarboxylation to 1,2-dimethylpyrrole (VI) took place merely on heating in cyclohexane. Substitution of methylene



chloride–pentane as the crystallization solvent resulted in excellent recoveries of pure acid (V) which was then converted to the barium salt and pyrolyzed under reduced pressure. The pyrolysate was easily separated into crystalline ketone (VII) (12% yield) and 1,2-dimethylpyrrole (49% yield). Späth and Tuppy (7) report a higher yield of crude ketone by pyrolysis of the lead salt on a much smaller (one one-hundredth) scale.

To effect the hydrogenation of the pyrrole rings in VII, platinum oxide in

glacial acetic acid was used. These are the conditions recently employed by Šorm (8) to prepare 1-methyl-2-acetonylpyrrolidine from the corresponding pyrrole compound without reducing the carbonyl group. When applied to VII, hydrogenation ceased after eight hours with the absorption of the theoretical four moles of hydrogen. The crude hydrogenation product was then separated by fractional distillation into four distinct fractions. Späth and Tuppy (7), using a palladium catalyst for the hydrogenation and working on an extremely small scale, observed only two fractions at this point.

Fraction B, which appeared to be most similar to natural cuscohygrine on the basis of boiling point and refractive index, was further examined by salt formation. With alcoholic picric acid, a picrate was obtained which, after three crystallizations from ethanol and one from water, melted at 216–217° and gave no depression on admixture with an authentic sample of cuscohygrine dipicrate[2] melting at the same temperature. The nitrate was prepared using alcoholic nitric acid, and repeated crystallization from absolute ethanol gave material whose melting point (203–204°) was not depressed by addition of cuscohygrine dinitrate (m.p. 204–205°).

In order to secure a pure sample of synthetic cuscohygrine as the free base, the remainder of fraction B was converted to the nitrate and subjected to a systematic fractional crystallization. The free base liberated from the pure nitrate so obtained distilled (bath temperature 110° and 0.1 mm. pressure) as a very pale yellow oil with n_D^{25} 1.4833. This refractive index is in fairly close agreement with that of natural cuscohygrine, variously reported as n_D^{17} 1.4864 (6), $n_D^{18.4}$ 1.4845 (2), and n_D^{20} 1.4832 (5).

The evidence presented above, we believe, demonstrates beyond doubt that a synthetic sample of cuscohygrine has been prepared. Also, the method of synthesis lends strong support to the formulation of its structure as I. However, the appearance of several other products in the final step prevents calling this synthesis an absolute proof of structure until the structures of these accompanying products have been established and the reaction shown to take a normal course. The question of the relative configuration of the two asymmetric carbon atoms also remains unsettled.

EXPERIMENTAL

All melting points are corrected, and all above 200° were taken in evacuated tubes. Microanalyses were performed by C. W. Koch and V. H. Tashinian.

N-Methylpyrrole. N-Methylpyrrole was prepared by pyrolysis of methylammonium mucate using the same procedure as in the preparation of pyrrole (9). With one mole of mucic acid to 2.5 moles of methylamine (as an approximately 10 *N* aqueous solution), 38–39% yields of N-methylpyrrole were obtained; b.p. 112–114°.

Ethyl 1-methyl-2-pyrroleacetate (III). The coupling between N-methylpyrrole and ethyl diazoacetate (10) was carried out according to the method of Sohl and Shriner (5). By extending the addition time of the N-methylpyrrole to three hours and using thoroughly dried reagents, the yield of ethyl 1-methyl-2-pyrroleacetate, allowing for recovered material, was increased to 71%; b.p. 105–110° at 6 mm.

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[2] We are indebted to Dr. R. L. Shriner who very kindly supplied us with a sample of natural cuscohygrine dinitrate from which all our derivatives for comparison were prepared.

Ethyl 1-methyl-2-pyrrolidineacetate (IV). A solution of 30 g. (0.18 mole) of ethyl 1-methyl-2-pyrroleacetate in 200 ml. of glacial acetic acid was hydrogenated at forty pounds pressure and room temperature using 3.0 g. of platinum oxide as catalyst. Hydrogenation ceased after the theoretical amount of hydrogen had been absorbed in three hours. The catalyst was filtered, the cooled filtrate was partially neutralized with 320 ml. of 12 *N* potassium hydroxide and the reaction mixture was then made basic to litmus with a saturated potassium carbonate solution. After extracting the solution with five 100-ml. portions of ether, the combined ether extracts were dried over potassium carbonate, filtered, and distilled to give 27 g., 88% yield, of ethyl 1-methyl-2-pyrrolidineacetate, b.p. 88–89° at 10 mm., n_D^{25} 1.4443 [reported (5) b.p. 88–89° at 10 mm., n_D^{20} 1.4465].

1-Methyl-2-pyrrolidineacetic acid. The ester (IV) was saponified by heating under reflux for three hours with a slight excess of barium hydroxide in three times its weight of water. Carbon dioxide was then bubbled in, the precipitated barium carbonate filtered, and the filtrate evaporated to dryness in vacuum. Crystallization of the hygroscopic residue from benzene gave 1-methyl-2-pyrrolidineacetic acid, m.p. 122–124° [reported (11) m.p. 124°].

The *picrate* of the *dimethylamide* was prepared as directed by Šorm (11), m.p. 144–145° (reported m.p. 147°).

Pyrolysis of the barium salt of 1-methyl-2-pyrrolidineacetic acid. An aqueous solution of the acid from 30 g. (0.175 mole) of ethyl 1-methyl-2-pyrrolidineacetate was treated with 390 ml. of 0.45 *N* barium hydroxide. The solution was evaporated and the thoroughly dried, finely ground residue was distilled at 260–300° (bath temperature) at 2–6 mm. to give 4 g. of distillate. Fractionation of this material resulted in four fractions, all of which gave positive tests for secondary amines (Hinsberg Test) and rapidly decolorized bromine in carbon tetrachloride and aqueous permanganate. No crystalline picrate could be obtained from any of the fractions.

1-Methyl-2-pyrroleacetic acid (V). The ester was saponified by heating under reflux for four hours with potassium hydroxide in 50% aqueous ethanol. After distilling the ethanol, the solution was cooled, acidified with concentrated hydrochloric acid, and the precipitated acid and potassium chloride filtered. The solid was thoroughly dried in a vacuum desiccator and then digested with four 100-ml. portions of ether. Evaporation of the combined and dried ether extracts gave the crude acid as light tan crystals, m.p. 102–105°. Crystallization from cyclohexane gave pure material but in very low recovery due to extensive decarboxylation. Methylene chloride–pentane was a much more satisfactory solvent. The purified acid melted at 110–112° [reported (12) m.p. 112°, 113°].

1,2-Dimethylpyrrole (VI). Heating 3 g. of 1-methyl-2-pyrroleacetic acid to 170° gave 2 g., 97% yield, of 1,2-dimethylpyrrole as distillate. On redistillation it boiled at 139–140°, n_D^{24} 1.4913.

Anal. Calc'd for C_6H_9N: C, 75.74; H, 9.54.
Found: C, 75.92; H, 9.43.

The *azobenzenesulfonic acid derivative* was formed by adding an ether solution of 1,2-dimethylpyrrole to an equimolar quantity of diazobenzenesulfonic acid dissolved in water. Vigorous shaking caused an immediate precipitate of the *p*-(1,2-dimethyl-5-pyrrylazo)-benzenesulfonic acid which was purified by dissolving in 0.1 *N* sodium hydroxide and reprecipitating with 0.1 *N* hydrochloric acid. After thorough washing and drying it melted at 273–275° with dec.

Anal. Calc'd for $C_{12}H_{13}N_3O_3S$: C, 51.60; H, 4.69; S, 11.48.
Found: C, 50.97; H, 4.59; S, 11.36.

1,3-Bis(1′-methyl-2′-pyrryl)-2-propanone (VII). The barium salt of 1-methyl-2-pyrroleacetic acid was prepared by neutralizing an aqueous solution of the acid with an equivalent amount of 0.37 *N* barium hydroxide, taking the usual precautions for exclusion of carbon dioxide. Evaporation of the solution at reduced pressure and heating the residue at 100° in a vacuum oven gave an anhydrous barium salt which was then well ground and dry-distilled from a 250 ml. Claisen flask in 30–40 g. batches. Distillation was carried out at 3 mm. pressure over the course of an hour as the bath temperature was raised from 270°

to 350°. From 263 g. (0.64 mole) of barium salt, a total of 80.6 g. of distillate was collected in the water-cooled receiver and acetone-Dry Ice trap. This material was dissolved in ether, combined, dried over sodium sulfate, and distilled to give 59 g. (49% yield) of 1,2-dimethylpyrrole, b.p. 139–140°, and 16.7 g. (12% yield) of 1,3-bis(1′-methyl-2′-pyrryl)-2-propanone (VII), b.p. 153–163° at 1–2 mm. The ketone crystallized in the receiver, and for analysis a sample was recrystallized several times from ethanol, m.p. 67–68° [reported (7) m.p. 68–69°].

Anal. Calc'd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46.
Found: C, 72.18; H, 7.24.

The *semicarbazone* was prepared by heating under reflux for one hour an ethanolic solution of the ketone, semicarbazide hydrochloride, and pyridine. Crystallization from aqueous ethanol gave material melting at 189–191° with dec. [reported (7) m.p. 194–197° with dec.].

Anal. Calc'd for $C_{14}H_{19}N_5O$: C, 61.51; H, 7.01.
Found: C, 61.71; H, 7.24.

Hydrogenation of 1,3-bis(1′-methyl-2′-pyrryl)-2-propanone (VII). A solution of 6.2 g. (0.029 mole) of ketone (VII) in 50 ml. of glacial acetic acid was hydrogenated at room temperature and thirty pounds pressure using 0.062 g. of platinum oxide catalyst. Hydrogen absorption ceased after four moles had been taken up in eight hours. The catalyst was filtered, the acetic acid evaporated at reduced pressure, and the cooled residue basified with saturated potassium carbonate solution. Extraction with six 50-ml. portions of ether, drying the combined ether extracts over sodium sulfate, and distillation gave 4.06 g. (63% yield) of a light yellow oil, b.p. 110–130° at 1 mm., n_D^{25} 1.5046. A total of 7.11 g. of crude distillate was then distilled through a one-meter Podbielniak column at 2.5 mm. pressure and the following fractions collected:

FRACTION	WT., G.	B.P. (2.5 MM.)	n_D^{25}
A	0.52	106–107°	1.4856
B	1 68	126–127°	1 4878
C	1.63	132–134°	1 4990
D	2.75	144–145°	1.5311

On the basis of physical constants and a preliminary examination of picrate formation, fraction B appeared to be the most similar to natural cuscohygrine and was investigated further.

Examination of fraction B. Picrate formation. A 0.2-g. sample of Fraction B, dissolved in 25 ml. of ethanol, was treated with 10 ml. of saturated alcoholic picric acid. The precipitated picrate was digested with 35 ml. of ethanol, cooled to room temperature, and filtered. After this process was repeated three times, the insoluble material was crystallized from water to give, after drying at 100° in vacuum, 0.14 g. (23% yield) of crystalline *picrate*, m.p. 216–217° with dec. On mixing with a sample of natural cuscohygrine dipicrate (m.p. 216–217°) there was no depression in the melting point.

Nitrate formation. To a solution of 0.2 g. of Fraction B in 5 ml. of commercial absolute ethanol was added a solution of nitric acid in ethanol (1 ml. of conc'd nitric acid in 10 ml. of absolute ethanol) until the mixture was acid to Congo Red. Cooling gave crystals which were recrystallized four times from 15-ml. portions of absolute ethanol and dried at 100° in vacuum; yield, 0.06 g., 19%, m.p. 203–204°. A mixture with natural cuscohygrine dinitrate (m.p. 204–205°) melted at 203–204°.

Free base. A 1.0 g. sample of Fraction B was converted to nitrate as described above and subjected to a systematic fractional crystallization. The 0.28 g. of pure nitrate obtained (m.p. 202–204°) was dissolved in 5 ml. of water, basified with 6 *N* sodium hydroxide, and extracted with four 5-ml. portions of ether. After drying and evaporating the ether, the residue was distilled at bath temperature 110° and 0.1 mm. pressure to give about 0.15 g. of pale yellow oil, n_D^{25} 1.4833.

SUMMARY

Cuscohygrine has been synthesized by a method that strongly supports 1,3-bis(1′-methyl-2′-pyrrolidyl)-2-propanone as its structure.

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[Contribution from the Department of Chemistry, Columbia University]

CASHEW NUT SHELL LIQUID. IV. ON THE HETEROGENEOUS NATURE OF THE MONOPHENOLIC FRACTION OF CASHEW NUT SHELL LIQUID. THE STRUCTURE OF THE MONO-OLEFINIC COMPONENT[1]

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The vesicatory properties of the saps of certain plants of the anacardiacea family, such as poison ivy, the Japanese lac tree, etc., and of the oily liquid which is extractable from the shell of the cashew nut (*Anacardium occidentale*), are due to the presence therein of phenolic compounds whose structures include a long unsaturated side chain attached to the phenol ring. Previous investigations (1, 2, 3) have in certain cases established the length and position of these alkenyl side chains, but little is known about the structural details of the unsaturation. There is no doubt, however, that the unsaturation of the side chain plays an important role both in the physiological properties (4, 5, 6) and the industrial uses (7) of these compounds.

In recent years large amounts of cashew nut shell liquid have been imported into this country from India and Brazil as a raw material for the manufacture of numerous industrial products (7). Thus there has become available a good source of the alkenyl phenols which can be used for structural investigations.

The oily liquid in the shell of the cashew nut appears to be almost completely phenolic in character; its major component is anacardic acid which is present to the extent of about 90% and the remainder is mainly cardol (8). Both Smit (9) and Backer and Haack (3), working with solvent-extracted cashew nut shell liquid, concluded that anacardic acid was a single substance with two olefinic bonds in the side chain, *i.e.*, a pentadecadienylsalicylic acid. The latter investigators reported it to be 2-carboxy-3-pentadecadienyl phenol. These authors also reported that anacardic acid readily loses carbon dioxide on heating to yield a single monophenol having the structure of a 1-hydroxy-3-pentadecadienyl benzene.

Cashew nut shell liquid has found important commercial usage as a raw material for the manufacture of certain resins and plastics. For commercial usage the liquid is obtained from the cashew nut shell by a process that involves heating the shell to a high temperature for several minutes in a vat of previously obtained shell liquid. During this process the shell liquid is held at a high temperature for several hours. Considerable decarboxylation of the anacardic acid takes place, and the product is a commercial raw cashew nut shell liquid which is mainly monophenolic in character, and contains a small amount [approximately 16%, (10)] of anacardic acid, cardol [a resorcinol derivative, (11)], and some

[1] For the third article of this series, see Wasserman and Dawson, *J. Am. Chem. Soc.*, **70**, 3675 (1948).

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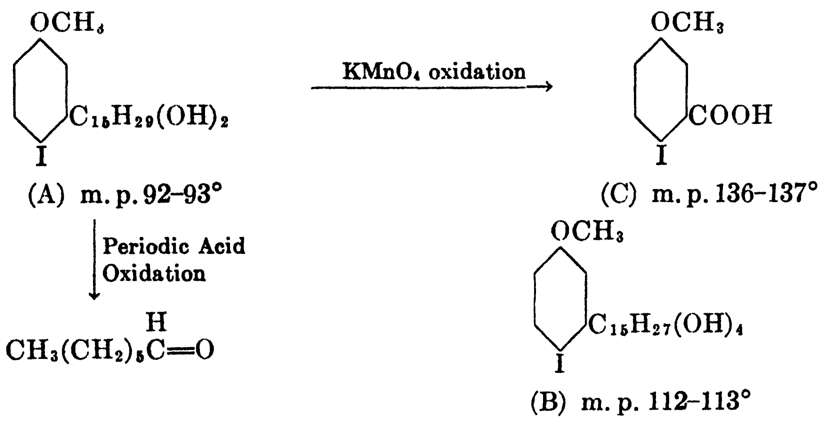
polymerized material. Wasserman and Dawson (12) have shown that the skeleton structure of the monophenol, cardanol, obtained by direct vacuum distillation of the raw commercial shell liquid, is the same as that established by Backer and Haack (3) for the monophenol obtained from solvent-extracted oil.[3]

It was the original purpose of this investigation to establish the positions of the two aliphatic double bonds in the side chain of the monophenolic component, cardanol, of the commercial shell liquid. However, attempts to obtain pure specimens of cardanol by repeated vacuum distillation of the commercial liquid gave products of continuously decreasing unsaturation. This observation, in conjunction with subsequent findings, suggested that the two double-bonded character of the monophenol, as originally isolated from the shell liquid, was the coincidental result of a mixture of monophenols having the same carbon structure but differing in their degree of unsaturation. The loss in unsaturation during distillation appeared to be due to selective polymerization of the more highly unsaturated components of the monophenolic mixture.

The experimental observations that definitely established the heterogeneous nature of the monophenolic fraction obtained by vacuum distillation of commercial cashew nut shell liquid were the result of an attempt to prepare a glycol derivative of the double bond by means of the Prévost reagent, silver iodo-



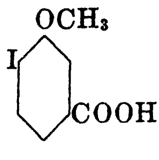
benzoate (14, 15, 16). As briefly reported elsewhere (17), treatment of the methyl ether of the monophenol from cashew nut shell liquid with silver iodobenzoate and subsequent hydrolysis of the benzoates, yielded on fractional crystallization from aqueous methanol two crystalline glycols (A and B) both of which contained iodine.

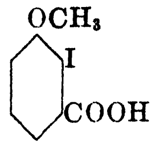
Both glycols showed no discoloration of bromine in carbon tetrachloride. Oxidation of the monoglycol (A) with periodic acid gave *n*-heptaldehyde which

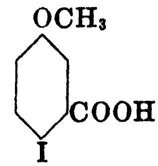
[3] Backer and Haack referred to the monophenol as "anacardol". However, the name "cardanol" is to be preferred for the monophenolic fraction resulting from the decarboxylation of anacardic acid, since Naidu (13) had previously used the name "anacardol" for a different phenol, $C_{18}H_{30}O$, found in marking-nut shell liquid. Additional reasons for preferring the name cardanol have been presented elsewhere (11).

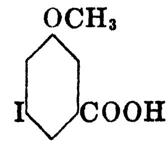
was identified as the 2,4-dinitrophenylhydrazone, while oxidation with alkaline permanganate gave an aromatic acid (C) containing one iodine atom in the nucleus.

Since it was known from previous work that the aliphatic side chain was *meta* to the methoxyl group in (A), four possibilities existed for the position of the iodine atom in the aromatic acid resulting from the oxidation. These were:


(a)


(b)

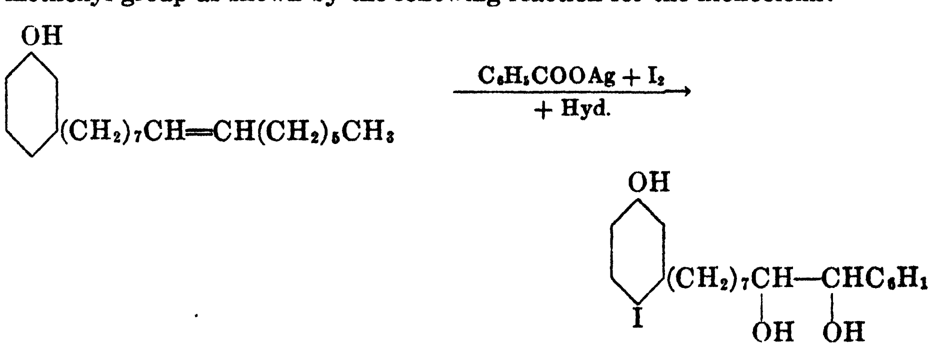

(c)


(d)

Of the four possible structures, (d) could be almost definitely eliminated because of the *ortho-para*-directing influence of both the methoxyl group and the alkyl side chain. Structure (b) seemed unlikely because it had been previously synthesized (18, 19) and reported as melting at 148–151°. For these reasons the two iodinated methoxybenzoic acids (a) and (c) were selected for synthesis, in order to establish the structure of the iodinated oxidation product.

Neither (a) nor (c) had been previously synthesized and the sequence of reactions used to prepare (c) from *meta*-cresol is illustrated in the Flow Sheet. By similar reactions the isomeric acid (a) was prepared from the nitrocresol (III) which had been separated from (II) by steam distillation (20, 21). The iodinated acid derived from the cashew nut shell liquid proved to be identical with the synthetic acid (c) as revealed by mixed melting points of the free acids and their amides (VIII).

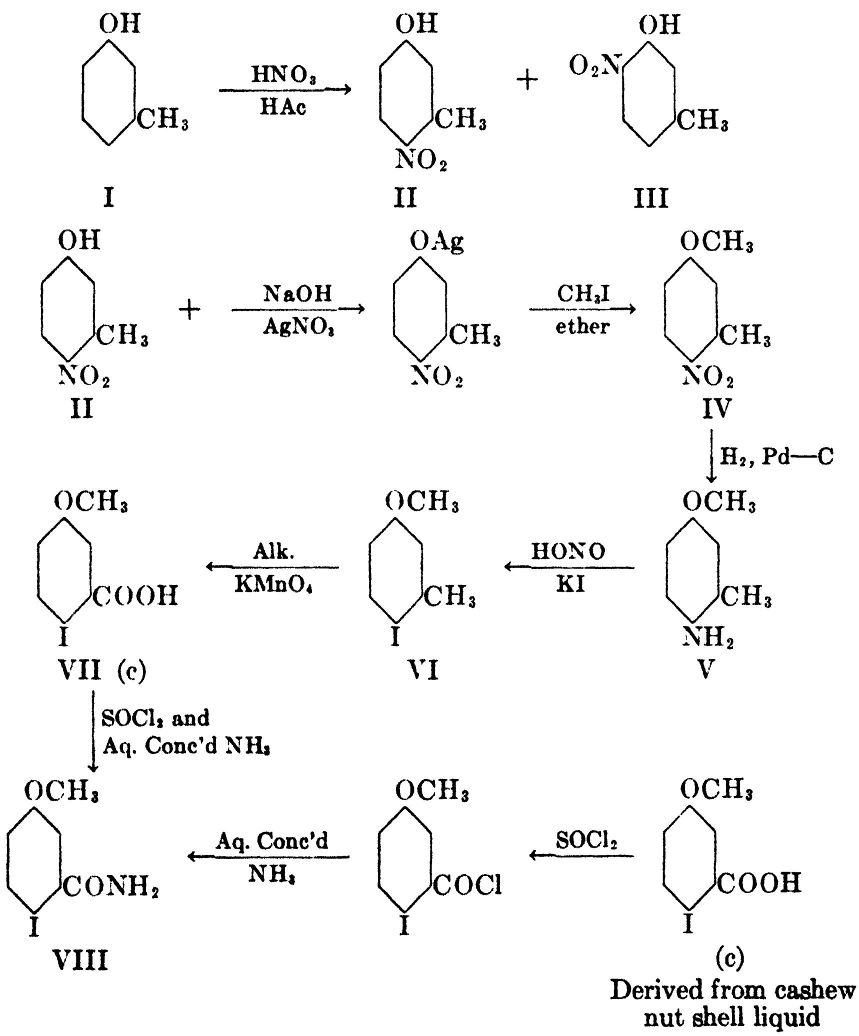
The above results establish that the monophenolic fraction of commercial cashew nut shell liquid contains at least two different olefinic components: one a monoölefin and the other a diölefin. The monoölefin is unsaturated in the 8–9 position of the side chain. During the hydroxylation of the double bonds by the Prévost reagent the benzene ring is iodinated in the *para* position to the methoxyl group as shown by the following reaction for the monoölefin:



In order to account for the average of two double bonds in the original monophenolic fraction of the shell liquid, it must be presumed that higher olefinic

components were also present. Although no serious attempt was made during the present investigation to isolate in pure form other glycols from the Prévost reaction mother liquors, these liquors on long standing deposited more crystalline material which melted differently than (A) or (B).

FLOW SHEET



As previously pointed out, Backer and Haack (3) working with a solvent-extracted oil, came to the conclusion that the monophenolic fraction was composed of a single compound possessing two aliphatic double bonds in its side chain. In view of the observed heterogeneous olefinic nature of the vacuum-distilled monophenolic fraction of commercial (heat-treated) cashew nut shell liquid, it seemed advisable to investigate the action of the Prévost reagent on

the monophenolic fraction of a solvent-extracted oil. Following the procedure described by Backer and Haack for the isolation of the monophenol, a phenolic fraction was obtained possessing an unsaturation equivalent to two aliphatic double bonds. Treatment with the Prévost reagent in the manner described above yielded a crystalline iodomonoglycol which proved to be identical with that obtained from the monophenolic fraction of the commercial (heat-treated) oil. These results establish the presence of a monoölefin in the vacuum-distilled monophenolic fraction of solvent-extracted oil possessing an average of two double bonds, and reveal, therefore, that the monophenolic fraction obtained by vacuum distillation of either the commercial (heat-treated) shell liquid or the solvent-extracted shell liquid is, in actuality, an olefinic mixture so composed as to possess under certain conditions an average of two double bonds.

TABLE 1

FRACTIONATION DATA

FRACTION	RATE OF DISTILLATION	BOILING POINT,[a]	VOLUME OF DISTILLATE	n_D^{30}	COLOR OF DISTILLATE	NO. DOUBLE BONDS
		°C.	cc.			
I[b, c]	1 drop/sec.	184	30	1.5040	light lemon	1.57
II[b, c]	1 drop/sec.	186	200	1.5050	light lemon	1.56
III[b, c]	1 drop/sec.	186	150	1 5050	light lemon	1.57
IV[b, c]	1 drop/sec.	188	200	1.5060	light lemon	1.58
V[b, c]	1 drop/sec.	190	150	1.5075	light lemon	1 57

[a] At 1.5 mm. pressure.
[b] Mantle temperature, 260°.
[c] Column temperature, 145°.

EXPERIMENTAL

RAW COMMERCIAL CASHEW NUT SHELL LIQUID

Decarboxylation and distillation. In order to decarboxylate the brown colored raw commercial cashew nut shell liquid, 1597 cc. of material was heated in a flask under 3 mm. pressure with an electrically heated mantle for one hour at 200°. The ground glass jointed flask was equipped with an electrically heated Vigreux column, condenser, and receiver. After the decarboxylation was finished, as evidenced by stoppage of bumping and splattering in the flask, the distillation was begun by raising the bath temperature to 260°. The material, boiling at 187–205° at 1.5 mm., was then collected. The volume of distillate collected which was yellowish in color was 860 cc.

In order to determine the unsaturation value of the distillate a 2.00-gram sample of the material in 50 cc. of ethyl acetate was reduced in an Adams shaker using 10% palladium on carbon as catalyst at 31° and 764 mm. pressure. The reduction came to a complete stop after 329 cc. of hydrogen had been absorbed which is in agreement with the theoretical value (328.4 cc.) for the reduction of two aliphatic double bonds under these conditions.

Fractionation of the monophenol. The fractionation was accomplished using a 34-in. Fenske helix-packed column, which was electrically heated and had a direct take-off.

An 850-cc. sample of the crude monophenol described above was fractionated at a rate of one drop per second by maintaining the mantle temperature at about 240° and the column temperature at about 140° at a pressure of 1.5 mm. The distillation yielded 20 cc. of fore-run boiling at 180–187° and 800 cc. of yellowish oil, which boiled at 187–194° at 1.5 mm. The

main fraction (800 cc.) was fractionated again at 1.5 mm. and yielded a fore-run of 40 cc boiling at 190–194° and 740 cc. of light lemon yellow-colored oil of b.p. 194–195° at 1.5 mm. The bath temperature was 240° throughout both distillations.

The above material (740 cc.) was then distilled for a third time yielding two fractions (II and III) having the same index of refraction. The fractionation data are given in Table I.

In order to determine if Fractions II and III were contaminated with any resorcinol compound, which is present to a small extent in raw commercial cashew nut shell liquid, each fraction was hydrogenated as described above and the hydrogenated mixture was processed as follows. The reduction mixture was filtered from the catalyst and the filtrate was concentrated by evaporation. The residue on cooling yielded white hairlike crystals of m.p. 51–51.5° in quantitative yield. Since a quantitative yield of saturated phenol of excellent melting point was obtainable from the hydrogenation of Fractions II and III, thus indicating that no contaminant was present, these fractions were therefore selected for further work.

Methylation of phenolic fractions II and III. A 150-g. sample of the monophenol of 1.57 double bonds was methylated in the customary manner using dimethyl sulfate and alkali. The oily product was extracted with Claisen solution to remove unmethylated phenol, dissolved in benzene, dried over magnesium sulfate and then fractionated. The fraction boiling at 195–196° at 2.5 mm. was collected. The yield was 120 g. (77%) of a colorless oil. The hydrogenation value indicated 1.56 double bonds.

Isolation of an iodomonoglycol (A) from the methyl ether of fractions II and III. A 10 g. sample of the methyl ether described above was added to a suspension of 35 g. of silver benzoate in 300 cc. of an anhydrous, thiophene-free benzene solution of 21 g. of iodine. The addition of the methyl ether was accompanied by the liberation of some heat and the violet iodine color soon changed to a lemon yellow on shaking. The resulting mixture was refluxed for two hours with occasional stirring and then cooled and filtered from the insoluble silver iodide. The benzene solution containing the benzoate esters was evaporated on a steam-bath *in vacuo* to leave a viscous oil. The oil was dissolved in 375 cc. of 80% ethanol containing 25 g. of KOH and refluxed for three hours on a steam-bath to hydrolyze the esters. The alcohol was then distilled until a heavy precipitate deposited in the flask. The residue was diluted with 50 cc. of water and extracted with three 50-cc. portions of ether. The ether extracts were washed with water until alkali free and then dried over magnesium sulfate, filtered, and evaporated. The oily residue was dissolved in a hot 4:1 methanol–water solution and allowed to cool slowly. Within a short time crystals appeared. The crystals were filtered and washed with cold methanol. The yield was 5.2 g. of material of m.p. 87–89° (the mother liquors were set aside for the isolation of the *diglycol* described below). Four recrystallizations from methanol gave a white, crystalline substance of m.p. 92–93° which showed no unsaturation with bromine in carbon tetrachloride. The presence of iodine in the molecule was established by qualitative tests and the analytical data given below. The compound analyzed for an *iodomonoglycol*.

Anal. Calc'd for $C_{22}H_{37}IO_3$: C, 55.35; H, 7.74; Mol. wt., 476.

Found: C, 55.55; H, 7.51; Mol. wt., (ebulliometric in CCl_4) 478.

Isolation of an iododiglycol (B). The methanol–water mother liquors from the previous reaction were evaporated to a small volume under vacuum on the steam-bath. The oily residue was dissolved in 50 cc. of benzene and dried over magnesium sulfate and filtered. The benzene was distilled off and the dried, residual oil was again dissolved in 10–15 cc. of benzene. The benzene solution was diluted with Skellysolve A[4] until precipitation was complete. A gummy precipitate separated which on standing in an icebox for two days turned semi-solid. The material was filtered and sucked as dry as possible. The solid was recrystallized three times from methanol and finally yielded a very small amount of white solid of m.p. 112–113°. The presence of iodine was established by qualitative tests and the analytical data given below for an iododiglycol.

[4] Hydrocarbon solvent, b.p. 83–100°F., supplied by Skelly Oil Co.

Anal. Calc'd for $C_{22}H_{37}IO_6$: C, 51.96; H, 7.28.
Found: C, 51.92; 52.01; H, 7.50; 7.43.

Oxidation of the iodomonoglycol (A) with potassium permanganate. Isolation of (c). In order to oxidize the iodomonoglycol (A) to an iodomethoxybenzoic acid and thereby locate the position of the iodine in the ring, 2.0 g. of the iodoglycol (A) was suspended in 250 cc. of water containing 10 g. of $KMnO_4$ and 2 cc. of 0.2 *N* NaOH. The mixture was refluxed for two hours or until the supernatant liquid was colorless. The hot solution was filtered through a Büchner funnel using Celite[5] as a filter aid. The MnO_2 precipitate was well washed with hot water. The colorless filtrate was acidified with conc'd H_2SO_4 until definitely acid to Congo Red paper and then cooled. Crystals appeared, which were filtered and then recrystallized from hot water. The yield of white needles of m.p. 136–137° was 380 mg. (32%). The analysis conformed to an *iodomethoxybenzoic acid.*

Anal. Calc'd for $C_8H_7IO_3$: C, 34.54; H, 2.51.
Found: C, 34.71; H, 2.77.

Oxidation of (A) with periodic acid. Isolation of n-heptaldehyde 2,4-dinitrophenylhydrazone. One gram of the iodomonoglycol (A) was dissolved in 100 cc. of ethanol. To this solution in a glass-stoppered Erlenmeyer flask at 35° was added 0.480 g. of periodic acid dissolved in 3 cc. of water. An immediate odor of aldehyde was detected. The reaction was allowed to stand at 35° for 15 minutes and then at room temperature (29°) for 2 hours. The solution was then diluted with twice its volume of water and an oil settled to the bottom of the mixture. This oil was extracted with ether and the extracts were evaporated to a small volume. The yellowish oil residue was then steam-distilled. A total of 150 cc. of distillate was collected and the aldehyde was extracted from this distillate using ether. The ether extract was evaporated and the residue remaining was dissolved in 100 cc. of 95% ethanol to which 0.50 g. of 2,4-dinitrophenylhydrazine was added. The mixture was refluxed until all was in solution. At this point 1 cc. of conc'd hydrochloric acid was added; the color then changed from red to yellow. Refluxing was continued for an additional 15 minutes, and the solution was cooled. A copious crop of yellow crystals deposited which were filtered, washed with cold ethanol, and dried. Yield 410 mg.; m.p. 106–107°. The mother liquors after concentration to one-half their volume gave an additional 60 mg. of material of m.p. 105°. Total yield 470 mg. (76%). Recrystallization of Crop I from 95% ethanol gave material of m.p. 106.5–107°. A mixed melting point with an authentic sample of the 2,4-dinitrophenylhydrazone of *n*-heptaldehyde of m.p. 105–108° showed no depression.

Anal. Calc'd for $C_{13}H_{18}N_4O_4$: C, 53.06; H, 6.12; N, 19.05.
Found: C, 53.23; H, 6.21; N, 19.10.

EXTRACTED CASHEW NUT SHELL LIQUID

The monophenol (methyl ether). Anacardic acid was obtained from the shells of the cashew nut, *Anacardium occidentale*, by solvent extraction and lead precipitation as previously described (3, 11). The resulting brown solid (m.p. 25–26°) absorbed 80.0 cc. of hydrogen per 0.555 gram in dioxane at 764 mm. pressure and 24° using Raney nickel as the catalyst (theoretical for two olefinic bonds, 79.0 cc.).

A 115-g. sample of the anacardic acid was decarboxylated in a small distilling-flask at 200° at 3 mm. pressure. The decarboxylation was finished after twenty minutes and the distillation of the phenol was begun by raising the bath temperature to 260°. The material boiling at 185–205° at 1.5 mm. was collected. The yield of yellowish oil was 50 g. or 50% (based on 115 g. of acid).

The decarboxylated yellow oil absorbed 334.4 cc. of hydrogen per 2.04 g. in 75 cc. of ethyl acetate at 758 mm. pressure and 30° in 3.5 hours using 0.5 g. of 10% Pd-carbon as catalyst (theoretical for two olefinic bonds, 335.0 cc.).

The monophenol was converted into the methyl ether using the same procedure as described previously for the methylation of the phenol obtained by fractionation of the commercial heat-treated oil. The hydrogenation of this methylated material also indicated

[5] A diatomaceous earth made by Johns-Manville and Co.

the presence of an average of two double bonds. (2.02 grams of methyl ether in 50 cc. of ethyl acetate using 0.2 g. of 10% Pd-carbon absorbed 325 cc. of hydrogen at 29° and 764 mm. of pressure; theory, for two double bonds, 326 cc.).

Isolation of iodomonoglycol (A). A 10 g. sample of the methyl ether just described was added to a suspension of 37 g. of silver benzoate in 250 cc. of dry, thiophene-free benzene containing 24.3 g. of I_2. By the procedure previously used for the isolation of the iodomonoglycol from the methyl ether obtained from heat-treated oil, a crystalline material melting at 92–93° was obtained in a yield of 1.5 g. A mixed melting point with the iodomonoglycol (m.p. 92–93°) resulting from the commercial oil showed no depression. This therefore proved the identity of the two materials and also established that the solvent extracted oil contained a monoölefinic component and therefore must also be a mixture.

SYNTHESIS OF IODOMETHOXYBENZOIC ACIDS

4-Nitro-5-methylphenol (II) and 2-nitro-5-methylphenol (III). The nitration of *meta*-cresol (I) and the separation of the nitro isomers (II and III) were carried out according to the directions of Staedel (20, 21).

4-Nitro-5-methylanisole (IV). A 5.0-g. sample of the 4-nitro-5-methylphenol prepared as described above was dissolved in 50 cc. of water containing 1.4 g. of sodium hydroxide. It was necessary to heat the mixture to 45° in order to attain complete solution. To this red solution was added slowly with stirring a solution of 6.0 g. of $AgNO_3$ in 15 cc. of water. A reddish precipitate formed. The mixture was then cooled to 5°, filtered, and the precipitate washed successively with cold water, methanol, and ether and finally dried in an air-drier.

The brownish precipitate of the silver salt of 4-nitro-5-methylphenol was suspended in 100 cc. of anhydrous ether and to this was added 8.4 g. of methyl iodide. The mixture was refluxed for 16 hours. The precipitate of AgI which at the end of this time had changed to a black color, was filtered and washed with ether. The filtrate was concentrated on the steam-bath to remove the ether and 10 cc. of 10% NaOH was added to the concentrate. This mixture was steam-distilled. A colorless oil separated from the steam-distillate and solidified on cooling (m.p. 52°). Recrystallization from Skellysolve A gave 5.0 g. (95%) of crystalline material melting at 55–56° as reported for 4-nitro-5-methylanisole (22).

4-Amino-5-methylanisole (V). A 5 g. sample of IV was reduced in 50 cc. of ethanol using 0.5 g. of 5% Pd-carbon. The reduction took up the theoretical amount of hydrogen (three moles of hydrogen for each mole of nitro compound) and was complete in 30 minutes. The solution was filtered from the catalyst and evaporated under reduced pressure to a yellowish oil. This material was not purified any further but used directly for the next step.

4-Iodo-5-methylanisole (VI). The yellowish oil (V) was dissolved in 36 cc. of water containing 8.8 g. of conc'd H_2SO_4. The solution was cooled to −5° and to it was added a cold solution of 2.3 g. of $NaNO_2$ in 15 cc. of water over a period of one hour with constant stirring and maintenance of temperature below 1°. After all was added, stirring and cooling was continued for an additional hour. To the cold solution of the diazonium salt was next added 9.96 g. of KI and the reaction mixture was allowed to stand overnight at room temperature. The next day the brownish solution was treated with an excess of sodium bisulfite to remove the excess iodine and then extracted with ether. The ether solution was evaporated to a reddish oil which was steam-distilled after the addition of 1.0 cc. of 10% NaOH. A yellowish oil separated in the distillate which on cooling solidified to a crystalline mass of m.p. 44–45°; yield, 4.7 g. or 60%.

4-Iodo-5-carboxyanisole (VII). To convert the methyl side chain of VI into a carboxyl group a 2.0 g. sample of VI was added to a solution of 2.6 g. $KMnO_4$ in 150 cc. of water containing 0.5 g. of NaOH, and the resulting solution was then refluxed until the supernatant liquid was decolorized. This took about three hours. The alkaline solution was filtered while hot from the manganese dioxide and the latter was well washed with hot water. The combined filtrates (alkaline) were then distilled under atmospheric pressure until no more oily drops of unreacted material were observed in the distillate. In this way, 1.5 g. of starting material was recovered. The water residue was made acid (*p*H 2) with conc'd

hydrochloric acid and cooled to 0° for three hours. Needles separated which were washed well with cold water. Yield, 300 mg. of white crystalline material, m.p. 135–136°. After two recrystallizations from hot water, it had m.p. 136–137°. The yield based on recovered starting material was 53.5%.

4-Iodo-5-amidoanisole (*VIII*). To convert the acid (VII) to the amide a 200-mg. sample was refluxed with 3 cc. of thionyl chloride for 30 minutes. The yellow solution was then added dropwise with stirring to 15 cc. of conc'd ammonia cooled to 0° with a Dry Ice-bath. A white precipitate settled out. This was filtered, washed well with cold water and recrystallized twice from water. Yield 195 mg. (98%); m.p. 189.5–190°.

Anal. Calc'd for $C_8H_8INO_2$: C, 34.65; H, 2.52.

Found: C, 34.60; H, 2.73.

2-Amino-5-methylphenol (*IX*). In order to convert III to the amine a 12 g. sample was reduced catalytically in 50 cc. of ethanol using 0.15 g. of 5% Pd-carbon. The reduction was completed in two hours and took up the theoretical amount of hydrogen. The solution was filtered from the catalyst and was colorless. However, as soon as the solution came into contact with the atmosphere it turned red. Nitrogen was then bubbled through to prevent any further oxidation. The solution was evaporated under reduced pressure to dryness and a brown solid was deposited in practically a quantitative yield.

2-Iodo-5-methylphenol (*X*). A 10-gram sample of IX was dissolved in 72 cc. of water containing 17 g. of conc'd sulfuric acid. The solution was cooled to −5° and a cold solution of 4.6 g. $NaNO_2$ in 30 cc. of water was added slowly with stirring in the course of one hour with maintenance of temperature below 1°. Stirring and cooling were continued for an additional hour after all of the nitrite had been added. To the cold solution of the diazonium salt 21 g. of potassium iodide in 20 cc. of water was next added. A large amount of foaming occurred and the solution was left standing overnight. The following day, the solution was treated with an excess of $NaHSO_3$ to remove the excess iodine and it was then extracted with ether. The ethereal solution was washed with aqueous potassium hydroxide and concentrated to an oil which was then steam-distilled. The steam-distillate was extracted with ether, dried over magnesium sulfate, filtered, and concentrated. A semi-solid deposited which weighed 10.5 g. This semi-solid was used directly for conversion to 2-iodo-5-methylanisole.

2-Iodo-5-methylanisole (*XI*). The crude phenolic compound (X) was methylated by dissolving an 8.0-g. portion in a hot alkaline solution containing 1.38 g. of NaOH in 50 cc. of water. To this was added slowly with stirring a solution of 5.5 g. of $AgNO_3$ in 15 cc. of water. A white precipitate separated which darkened on standing. The insoluble silver salt was filtered, washed with water, methanol, and ether and dried in air.

The dry silver salt was suspended in 100 cc. of anhydrous ether containing 12 g. of methyl iodide and refluxed for 8 hours. The solution was filtered and the yellowish filtrate evaporated to an oil which weighed 9.0 g.

The residual oil was treated with 1.0 cc. of 10% NaOH solution and steam-distilled. A colorless oil collected in the distillate. A large amount of a yellow insoluble solid remained in the distilling flask. The distillate was extracted with ether and the ether extracts dried over magnesium sulfate, filtered, and evaporated to dryness. The yield of colorless oil was 2.0 g.

2-Iodo-5-carboxyanisole (*XII*). The methyl side chain of XI was oxidized by suspending 2 g. of the material in 250 cc. of water containing 2.57 g. $KMnO_4$ and 0.2 g. of KOH. The mixture was refluxed for 12 hours or until the color in the supernatant liquid had disappeared. The hot solution was filtered and extracted with benzene to remove any unreacted material. The excess benzene was removed from the water solution under vacuum. Conc'd hydrochloric acid was added to the aqueous solution until it was definitely acid to Congo Red paper and then it was cooled to 0°. White crystals deposited, which were washed with water, and recrystallized from hot water. Yield 2.0 g. (86%); m.p. 210–213°.

Anal. Calc'd for $C_8H_7IO_3$: C, 34.56; H, 2.52.

Found: C, 34.67; H, 2.64.

ACKNOWLEDGMENT

The authors are indebted to the Irvington Varnish and Insulator Company of Irvington, New Jersey, for the supply of commercial cashew nut shell liquid, and for their helpful interest in this investigation. The authors also wish to thank Miss Lois May who carried out the microanalyses reported in this communication.

SUMMARY

The methylated monophenol obtained from commercial cashew nut shell liquid both by vacuum-distillation and by solvent-extraction contains the same monoölefinic component. The isolation of an iodomonoglycol, by means of the Prévost reagent, proves the heterogeneous nature of these substances, for it must be assumed that higher olefinic components were also present in the oil in order to account for the average of two double bonds in the starting material.

The monoölefinic component is unsaturated in the 8–9 position since *n*-heptaldehyde was isolated after periodic acid oxidation of the corresponding glycol.

The complete structure of the iodomonoglycol was shown to be 3-(8′,9′-dihydroxypentadecyl)-4-iodoanisole. The position of each of the substituents on the benzenoid ring was proven by degradation and synthesis.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

THERMAL DEHYDRATION OF SUGARS

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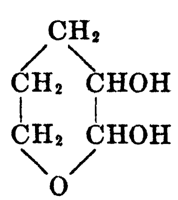
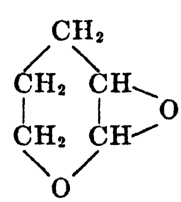
Pictet and Castan (1) reported that α-D-glucose readily lost one mole of water at 150° under 15 mm. pressure to yield a crystalline product which was named α-glucosan. These workers, and later Cramer and Cox (2) working in the same laboratory, brought forth evidence supporting a 1,2-anhydroglucose structure for this material.

Examination of this evidence, however, shows it to be in conflict with established facts. From their α-glucosan, on treatment with sodium methoxide in methanol, they obtained a substance which was considered to be 2-methyl-D-glucose, since it reduced Fehling's solution but gave no phenylosazone (1). Actually, however, 2-methyl-D-glucose has since been shown (3) to give D-*arabo*-hexose phenylosazone when treated with phenylhydrazine and acetic acid at room temperature. Their trimethyl-α-glucosan (2), which was synthesized by treatment of an aqueous solution of α-glucosan at 35–40° with methyl sulfate and sodium hydroxide solution, was hydrolyzed on boiling with water into trimethyl-D-glucose. The phenylosazone of the latter melted at 163–164°, differing from either of the two forms (m.p. 80–82° and 137–138°) of the phenylosazone of 3,4,6-trimethyl-D-glucose (4) or of the phenylosazone (m.p. 70–72°) of 3,5,6-trimethyl-D-glucose (5). Unless another crystalline modification of one of these osazones exists, the trimethyl ether reported by Cramer and Cox is not of the structure assigned.

When α-glucosan was heated with methyl iodide and methanol in a sealed tube at 130°, and the resulting methyl iododesoxyglucoside reduced with sodium amalgam, a sirupy product was formed which was regarded as methyl 2-desoxy-D-glucoside, since on acetylation with acetic anhydride in pyridine it yielded a crystalline triacetate of m.p. 96–97°, the same melting point as that previously found (6a) for methyl triacetyl-2-desoxy-D-glucoside. This supports the structure of α-glucosan as 1,2-anhydro-D-glucopyranose. It so happens, however, that 1,2-anhydro-3,4,6-triacetyl-D-glucose has been prepared otherwise by Brigl (6b) by treatment of 3,4,6-triacetyl-D-glucosyl chloride in benzene with ammonia. Both Brigl's compound and 1,2-anhydro-D-mannose (7) have been shown to be very sensitive toward water or methanol. This is in marked contrast to the reported stability of α-glucosan and its tribenzoate. Several groups of workers have reported unsuccessful attempts to prepare crystalline α-glucosan (8).



I



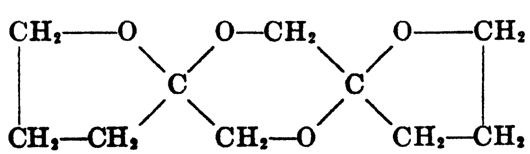
II

Racemic 3,4-didesoxyaldopentose (I), prepared by hydroxylation of dihydropyran (9), seemed to offer possibilities for the elucidation of this general problem. If any tendency exists for the formation of a 3-membered ring on heating glucose, it follows that the didesoxyaldopentose should show a similar tendency with the resultant formation of II. Accordingly, I was pyrolyzed under conditions comparable to those used with glucose. Like glucose, this model compound also lost water on heating to 150° under reduced pressure, or when xylene was distilled from it. Nothing resembling II was found, however. Instead, certain distillable products were obtained, namely, tetrahydrofurfural and two crystalline isomers (m.p. 103° and 190°) of formula $C_{10}H_{16}O_4$. There was a non-volatile water-soluble residue of mean molecular weight near 300, representing over half of the starting material.

The weight of the 103°-compound was about one-fifth that of the original (I). It was indifferent toward acetic anhydride in pyridine or toward Benedict's solution; hence it contained no free hydroxyl group or aldehyde group. It was stable to alkali but was hydrolyzed rapidly by dilute mineral acid to a reducing substance which gave both a 2,4-dinitrophenylhydrazone and a 2,4-dinitrophenylosazone. The 2,4-dinitrophenylhydrazone was isomeric with the corresponding derivative obtained from I, whereas the osazones were identical. This suggests that the hydrolysis product was 3,4-didesoxyketopentose (III), and that its crystalline precursor which melted at 103° was IV. Two names for IV are 2,5-bis(trimethyleneoxy)-1,4-dioxane and 1,6,12,13-tetraoxadispiro-[4·2·4·2]tetradecane.[1] The identical ring system occurs in the "Difructose Anhydride I," of Jackson and Goergen (10). In contrast to the ease of hydrolysis of our compound, however, theirs showed marked resistance to acid hydrolysis.

$$HOCH_2COCH_2CH_2CH_2OH$$

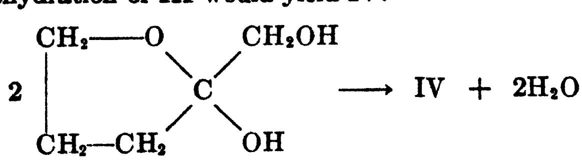
III



IV

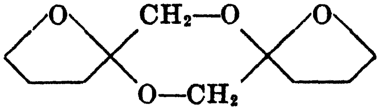
To explain the formation of IV from I, it is believed that the acyclic form of I first undergoes enolization to $HOCH_2CH_2CH_2\underset{\displaystyle OH}{\underset{|}{C}}{=}CHOH$, then changes to III.

Bimolecular dehydration of III would yield IV:

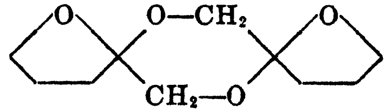


[1] In the course of our work we learned that Samuel Swadesh and A. P. Dunlop were working on the same substance, obtained from a different source (*J. Org. Chem.*, following article).

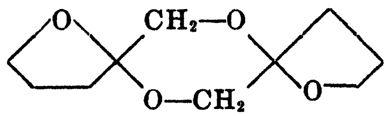
It is possible for IV to exist as a racemic pair,



and

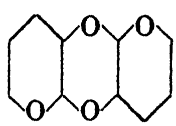


or a *meso* form,



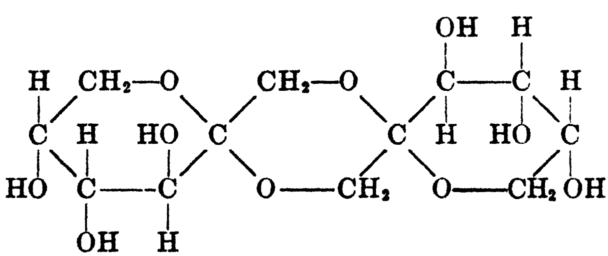
Which of these is the substance under discussion cannot be stated.

The second crystalline compound, m.p. 190.5°, was also nonreducing and stable to alkali. It was hydrolyzed very slowly by hot mineral acid to a substance which gave the 2,4-dinitrophenylosazone of I. It also may have been of structure IV (either the racemic pair or the *meso* compound), but since the new 2,4-dinitrophenylhydrazone was not obtained it also may be a dimeric anhydride of I, such as

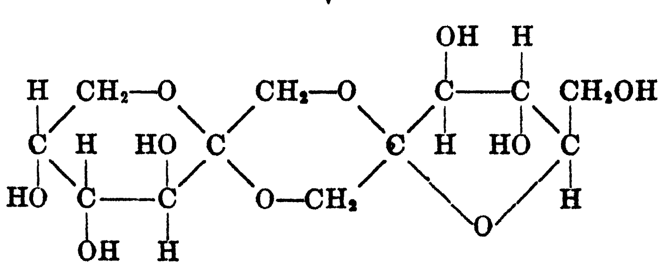


Unfortunately, the osazone is not a critical derivative and conditions were not found for the preparation of a hydrazone.

Related to these observations is the known fact that on heating concentrated solutions of D-fructose, it is possible to effect a similar kind of anhydrization. Two crystalline products have been obtained (11), one of which possesses structure V. Structure VI has been proposed for the other.



V



VI

Attempts to distill the higher molecular weight pyrolysis products from the 3,4-didesoxyaldopentose resulted in the production of considerable quantities of tetrahydrofurfural; it is, therefore, possible that all the tetrahydrofurfural

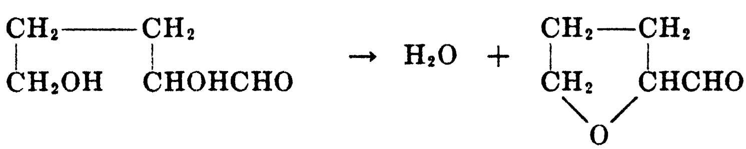
TABLE I

MELTING POINTS OF DERIVATIVES, °C.

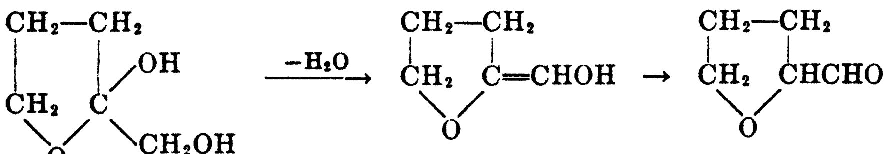
PARENT COMPOUND	A	B	C	D	E
I	174.5–175.5[b]	132–133	242[b]	128.5–129.5[a]	246–247[a]
III	154–157	164–165	242	—	—
Tetrahydrofurfural	—	133–134	242	146–147	—

[a] Unpublished results obtained in work with Miss Patricia Craig.
[b] Ref. 9.
A. Bis-3,5-dinitrobenzoate.
B. 2,4-Dinitrophenylhydrazone.
C. 2,4-Dinitrophenylosazone.
D. p-Nitrophenylhydrazone.
E. p-Nitrophenylosazone.

arises in this fashion. It is equally possible, however, that some of the tetrahydrofurfural is formed directly from the 3,4-didesoxyaldopentose as follows:



or indirectly *via* the rearrangement product (IIIa).



IIIa

In connection with this study, tetrahydrofurfural p-nitrophenylhydrazone was prepared. Synthesis of the benzylphenylhydrazone was repeated, and its melting point was found to be higher than that reported in the literature. It was also demonstrated that on heating in acid solution with 2,4-dinitrophenylhydrazine, tetrahydrofurfural gives the same 2,4-dinitrophenylosazone as I and III. Thus the tetrahydrofuran ring is subject to ready hydrolytic cleavage. In Table I the constants of these and other derivatives are collected.

Epoxy compounds may be synthesized by the action of peroxybenzoic acid on olefins. Conceivably, therefore, 2,3-epoxytetrahydropyran (II) would be formed in this manner from dihydropyran. In studying this synthesis, we found that the bulk of the reaction product was a thick, non-volatile oil, which was insoluble in water. There was produced, however, a poor yield of an unstable,

volatile, sparingly-soluble liquid which seemed to be the desired epoxy compound. The properties of these products differ from the substances described above which were isolated following the pyrolysis of I.

In view of the above considerations, the pyrolysis of glucose was reinvestigated. It was proposed to heat the sugar under diminished pressure until a definite quantity of water was detached, then to propionylate the mixture. If the change was merely one of intramolecular dehydration as proposed by Pictet and coworkers, the propionic derivative should be completely distillable at about 200° (0.001 mm.). Monosaccharide propionates are known (12) to distil in this range. These observations were made in the present study.

(a) The loss of water from α-D-glucose under a given pressure increases steadily with time even beyond one mole. In our experiments the rate was considerably slower than that reported by Pictet. Crushed soft glass or Pyrex glass accelerates the loss of water as does diminished pressure.

(b) If an anhydroglucose is present in the lower molecular weight material the bulk of it is stable to methanol (authentic 1,2-anhydroaldoses give methyl aldosides at room temperature with dry methanol), but is converted to glucose by dilute acid and to glucose esters by acid anhydride in pyridine.

(c) Contrary to Pictet and Castan's report, β-D-glucose dehydrates as readily as α-D-glucose.

(d) Higher molecular weight materials are formed in this process, although when one mole of water has been removed, one-fourth of the product is still monosaccharide, but crystalline glucose as such was not recovered if more than two-thirds of a mole of water had been removed. These condensed materials have mean molecular weights in the di- and tri-saccharide ranges, this molecular weight increasing with the loss of water. Even the methanol-soluble product is partly polymeric, the higher molecular weight portion being resistant to hydrolysis by acid. The propionates of the higher molecular weight material could not be distilled in a molecular still, so probably contained little anhydrodisaccharide hexapropionate. Thus, although there is no direct evidence that glucose changes into a spiro compound in the way that I changes into IV, it must be remembered that the major product from I was not IV, but a material of greater complexity.

(e) An interesting aspect of the present study was the isolation of an anhydrous complex, *sodium chloride diglucose* of m.p. 168°, $(C_6H_{12}O_6)_2 \cdot NaCl$, by direct crystallization from methanol. A hydrated form of this complex has been known for over a century. Röhmann (13) obtained such a hydrate and from it by desiccation at 110° secured the anhydrous complex which may have been the same as our material. He reported no melting point, however.

Recent work on the pyrolysis of D-glucose at 170–210° has been reported by Puddington (14). He also found that dehydration continues after one mole of water is detached but that the first half mole is lost at a faster rate than otherwise. Carbon dioxide and carbon monoxide were produced. The reaction product was an amber-colored glass and no evidence was found for a crystalline C_6 α-glucosan. In view of the rapid dehydration involving 0.5 mole of water,

Puddington suggests that the first step in this reaction is a condensation dimerization: $2C_6H_{12}O_6 \rightarrow C_{12}H_{22}O_{11} + H_2O$. Our observation that dextrose was still present in most of our runs, and that monosaccharide remained even after the loss of one mole of water, is difficult to reconcile with this suggestion. His data however, are not incompatible with our suggestion that still higher condensations ensue.

EXPERIMENTAL

3,4-Didesoxyaldopentose. The reaction between hydrogen peroxide and 200 g. of dihydropyran in *tert*-butyl alcohol was carried out in a manner identical to that of Hurd and Kelso (9). After removal of the *tert*-butyl alcohol under reduced pressure, the product was warmed on the steam-bath for one hour with 400 cc. of 1 *N* hydrochloric acid, then left overnight at room temperature. After neutralization, the solution was concentrated to a thick oil at 90° under 15 mm. pressure. The organic matter was extracted into acetone, the solution dried, and the solvent distilled. The 169 g. of oil was acetylated with acetic anhydride in pyridine and the resulting acetate distilled under 1 mm. pressure. Refractionation of the distillate gave 125 g. (26% over-all yield) of ester, b.p. 96–100° under 1 mm. and having n_D^{27} 1.443 to 1.444. In addition to higher- and lower-boiling cuts, there was 60 g. of much higher-boiling residue. The 60 g. was deacetylated, hydrolyzed at 90° for two hours with 1 *N* hydrochloric acid and the product recovered and acetylated as above. One-third of the acetate boiled at 95–125° (2 mm.), n_D^{25} 1.4420 to 1.4458. The remainder was still of higher molecular weight.

To a solution of 61.8 g. of the 3,4-didesoxyaldopentose diacetate in 250 cc. of absolute methanol at 3° was added 0.2 g. of sodium. The solution stood for six hours at 0°, then was neutralized by the dropwise addition of concentrated hydrochloric acid. The product was freed of methanol and methyl acetate and was again put through the deacetylation procedure. The resulting oil was dissolved in dry acetone, the salts separated, and the solvent removed. The didesoxypentose was extracted into dry ether, leaving a syrupy residue. The soluble material was a nearly colorless oil (30 g., 84% yield), n_D^{25} 1.480.

2,5-Dihydroxypentanal 2,4-dinitrophenylhydrazone. A hot concentrated methanol solution of 2,4-dinitrophenylhydrazine hydrochloride was added slowly to an agitated ice-cold solution of 1.34 g. of 3,4-didesoxyaldopentose in 10 cc. of water. The addition was continued, with intermediate concentration below room temperature in an air stream and filtration, until no more derivative could be obtained. The 3.5 g. of product melted up to 72°. Recrystallization of this from methanol removed 0.4 g. of 2,4-dinitrophenylhydrazine, and after two more recrystallizations the tiny light-yellow plates melted at 132–133° when immersed at 110°.

Anal. Calc'd for $C_{11}H_{14}N_4O_6$: C, 44.29; H, 4.74; N, 18.78.
Found: C, 44.21; H, 4.82; N, 18.96.

When heated with methanol containing a trace of hydrochloric acid, or with 2,4-dinitrophenylhydrazine in methanol, it gave the *2,4-dinitrophenylosazone* reported by Hurd and Kelso (9), m.p. 242°.

Pyrolysis of 3,4-didesoxyaldopentose. The sugar (22.3 g.) was placed in a 50-ml. Claisen flask fitted with a capillary connected to a nitrogen source and set up for vacuum distillation. When the system was evacuated to 17 mm. pressure, and the oil-bath was heated to 145°, distillation commenced. The bath temperature was raised during one hour to 155° and during the next two hours to 180°. In this time 2.8 g. of distillate collected (cut 1), and the cold-trap (−78°) in the system collected 2.2 g. of liquid. Further heating was carried out under 1 mm. pressure. In the bath temperature range 130–170° (vapor 75–80°), 3.7 g. of distillate was obtained (cut 2) and when the temperature was raised to 185°, a further 0.9 g. (cut 3) distilled. A further 0.6 g. collected in the cold-trap. The residue in the flask weighed 12 g.

A sample of cut 1 when reacted with 2,4-dinitrophenylhydrazine hydrochloride in methanol at room temperature gave the corresponding osazone of 2,5-dihydroxypentanal and the *2,4-dinitrophenylhydrazone* of *tetrahydrofurfural*. The latter had the form of fine yellow needles when recrystallized from methanol, m.p. 133–134° when immersed at 115°.

Anal. Calc'd for $C_{11}H_{12}N_4O_5$: C, 47.13; H, 4.32; N, 19.99.

Found: C, 47.29; H, 4.18; N, 20.70.

This derivative has been reported (16) as melting at 131° and 136°.

A concentrated solution of cut 2 in ether when chilled deposited 2.5 g. of a compound of m.p. 103°, and about 0.2 g. of a compound sparingly soluble in ether, m.p. 190.5°. Cut 3 yielded 0.2 g. each of the 103° compound and the 190.5° compound. The liquids from the mother liquors gave the 2,4-dinitrophenylosazone of the starting material and the 2,4-dinitrophenylhydrazone of 3,4-didesoxyketopentose (see below). When these liquids were distilled under 1 mm. pressure, approximately 1.5 g. of the 103° compound was obtained from the distillate, and more high-boiling residue was formed. In all, 4.1 g. of the 103° compound was isolated.

Tetrahydrofurfural. The liquid in the cold-trap consisted of water and a water-soluble, ether-soluble liquid. The latter gave a positive Schiff test and had an odor similar to acetaldehyde. It gave the 2,4-dinitrophenylosazone, m.p. 242°, and in addition to the 2,4-dinitrophenylhydrazone of tetrahydrofurfural, the following derivatives of that aldehyde were prepared.

Benzylphenylhydrazone. Faintly colored needles from methanol, m.p. 74–75°.

Anal. Calc'd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.97.

Found: C, 77.17; H, 7.27; N, 10.09.

Tetrahydrofurfural benzylphenylhydrazone is reported (17) to melt at 67°.

p-Nitrophenylhydrazone. Yellow needles from methanol, m.p. 146–147° when immersed at 130°.

Anal. Calc'd for $C_{11}H_{13}N_3O_3$: C, 56.15; H, 5.57; N, 17.86.

Found: C, 56.19; H, 5.67; N, 17.99.

When 0.15 g. of tetrahydrofurfural 2,4-dinitrophenylhydrazone was heated for one and one-half hours with a methanol solution of 2,4-dinitrophenylhydrazine hydrochloride, 0.13 g. of fine needles was obtained. After one recrystallization from nitromethane, these melted at 242° and showed no mixed m.p. depression when mixed with the 2,4-dinitrophenylosazone of 3,4-didesoxypentose.

2,5-Bis(trimethyleneoxy)-1,4-dioxane. The compound melting at 103° had the form of thick, nearly rectangular plates.

Anal. Calc'd for $C_{10}H_{16}O_4$: C, 59.99; H, 8.06; Mol. wt. 200.

Found: C, 60.08; H, 8.05; Mol. wt. (cryoscopically in benzene), 191.

It could be readily recrystallized from ether, was very soluble in methanol and sparingly soluble in water. It reduced hot neutral permanganate, and after a short induction period, it rapidly decolorized a solution of bromine in chloroform with hydrogen bromide evolution. It was inert to hot Benedict's reagent and was unchanged after standing for sixteen hours with acetic anhydride in pyridine. Dilute mineral acid readily hydrolyzed the compound to 3,4-didesoxyketopentose.

3,4-Didesoxyketopentose 2,4-dinitrophenylhydrazone. A 0.25-g. sample of the 103°-compound was heated with 2 cc. of water containing one drop of concentrated hydrochloric acid until it had completely dissolved (one minute). The solution was cooled in ice, and a hot saturated solution of 0.5 g. of 2,4-dinitrophenylhydrazine in methanol containing hydrochloric acid was added slowly while the mixture was agitated. The 0.65 g. of product when recrystallized from methanol separated as fine yellow needles, m.p. 164–165° when immersed at 140°.

Anal. Calc'd for $C_{11}H_{14}N_4O_6$: C, 44.29; H, 4.74; N, 18.78.

Found: C, 44.33; H, 4.83; N, 18.5.

When 0.1 g. of the above derivative was heated with a methanol solution of 0.1 g. of 2,4-dinitrophenylhydrazine as its hydrochloride, a slow precipitation of the 2,4-dinitro-

phenylosazone started. A total of 0.1 g. was obtained melting at 240°. It did not depress the melting point of an authentic sample prepared from 3,4-didesoxyaldopentose.

3,4-Didesoxyketopentose bis-3,5-dinitrobenzoate. A 0.3-g. sample of the 103° compound was hydrolyzed as described above, the acid neutralized, and the bulk of the water removed under reduced pressure. By use of ether there was extracted 0.33 g. of oil from the residue. This was dissolved in 2 cc. of pyridine, 1.5 g. of 3,5-dinitrobenzoyl chloride was added, and the solution was left overnight. The mixture was then dissolved in chloroform, washed free of pyridine, acid, and acid chloride, dried, and the chloroform distilled away. The product was a glass weighing 0.85 g. This readily crystallized from acetone, from which it was obtained microcrystalline. After repeated recrystallization, it melted at 154–157° when immersed at 135°.

Anal. Calc'd for $C_{19}H_{14}N_4O_{12}$: C, 45.06; H, 2.79; N, 11.06.
Found: C, 45.38; H, 2.89; N, 11.04.

3,4-Didesoxyketopentose dibenzoate. The oil from the hydrolysis of 0.3 g. of the 103°-compound when left overnight with 0.9 g. of benzoyl chloride and 3 cc. of pyridine gave 0.6 g. of ester. After long standing, this crystallized in part. The product after two recrystallizations from a mixture of ether and petroleum ether had the form of long needles, m.p. 67°.

Anal. Calc'd for $C_{19}H_{18}O_5$: C, 69.93; H, 5.56.
Found: C, 70.05; H, 5.56.

The high-melting compound. After recrystallization from methanol, this melted at 189.5–190.5° when immersed at 165°.

Anal. Calc'd for $C_{10}H_{16}O_4$: C, 59.99; H, 8.06; Mol. wt., 200.
Found: C, 59.88; H, 8.22; Mol. wt., 188.

The compound had a slight solubility in hot water, and could be recovered unchanged from solution in hot Benedict's reagent. After 100 mg. of this compound had been heated for three hours on the steam-bath with 3 cc. of methanol, 2 cc. of water, and two drops of concentrated hydrochloric acid, 75 mg. was recovered unchanged. The aqueous solution of the hydrolysis products, when warmed on the steam-bath with 2,4-dinitrophenylhydrazine hydrochloride gave 0.1 g. of *3,4-didesoxypentose 2,4-dinitrophenylosazone,* m.p. 242°. The compound could be recovered unchanged from solution in chloroform containing bromine.

Run 2. The bulk of the *o*-xylene was distilled from a mixture of 18.5 g. of 3,4-didesoxyaldopentose and 125 cc. of *o*-xylene over a period of two and one-half hours. Approximately 0.8 cc. of water distilled with the *o*-xylene. After removal of the last of the *o*-xylene under reduced pressure, an attempt was made to distill the products under 11 mm. pressure at bath temperatures up to 145°, without success. The cold-trap (−78°) collected 0.4 cc. of water. Another 75 cc. of the hydrocarbon was then distilled from the residue. It carried with it 0.2 cc. of water, making a total of 1.4 g. (50 mole per cent) of water collected. The water and the *o*-xylene contained a reducing substance which gave the *2,4-dinitrophenylosazone* of *3,4-didesoxypentose.*

The residue was distilled under reduced pressure.

(A) 6.6 g. b.p. 135° at 11 mm. n_D^{25} 1.4751
(B) 0.6 g. b.p. 90° at 1 mm. n_D^{25} 1.4763
(C) 1.0 g. b.p. 90–100° at 1 mm.

The cold-trap (−78°) in the system collected 0.4 g. of water containing a reducing substance, and some *o*-xylene.

When an attempt was made to redistill (A) the distillate crystallized in the condenser. A concentrated ether solution of the cut yielded 2.6 g. of 2,5-bis(trimethyleneoxy)-1,4-dioxane. When the oil from the mother liquors was redistilled under 1 mm. pressure, the distillate yielded approximately 1 g. of the same compound.

Less volatile pyrolysis products. Twenty-five grams of residues from the distillation of pyrolysis products from several runs were submitted to distillation under 1 mm. pressure in a modified Claisen flask with a very low side arm. A stream of nitrogen was introduced

through a capillary. As the bath temperature was slowly raised to 205°, a total of 5.4 g. of distillate collected. The last cut had the molecular weight 163 ± 10. Less than 0.1 g. of the 103°-compound was obtained from the first cut, the remaining distillate being an oil. The 16.5 g. of residue was a viscous reddish-brown oil of mol. wt. 275 ± 15, insoluble in ether but soluble in water. The cold-trap (−78°) collected 2.5 g. of a mobile liquid. This contained water, and gave tetrahydrofurfural derivatives equivalent to 1 g. of the aldehyde.

Action of hydrogen chloride on 3,4-didesoxyaldopentose. Dry hydrogen chloride was bubbled for one minute into 2.3 g. of the sugar. A red color developed quickly. The mixture thickened during five hours and crystallized in part. The product was then extracted with chloroform which dissolved the crystals and part of the oil. The chloroform solution was washed with aqueous sodium carbonate, dried, and the solvent distilled away. The resulting oil deposited crystals which were separated by dissolving the oil in ether. After one recrystallization from methanol, the 0.13 g. of crystals melted at 189° and proved identical with the compound melting at 190.5° obtained by pyrolysis.

2,3-Epoxytetrahydropyran. A solution of 52 g. (0.38 mole) of peroxybenzoic acid in 610 cc. of chloroform was prepared (18). Dihydropyran (29 g., 0.35 mole) was added during forty-five minutes to the above solution while the temperature of the mixture was kept below 5°. The reaction was exothermic. The solution was left at −6° for sixteen hours, at the end of which time the peroxybenzoic acid was almost completely gone. The chloroform solution was washed thoroughly with sodium carbonate solution, dried, filtered, and distilled. When the residual volume reached 150 cc., acid appeared in the distillate. The solution was washed thoroughly with sodium bicarbonate solution to remove benzoic acid. After drying and filtering, the solvent was distilled. The residual liquid was distilled under 9 mm. pressure:

Cut 1, b.p. 75–79°, 8.2 g. of nearly water-white liquid which turned yellowish-brown overnight. The residue was a brown oil which contained acid. It was dissolved in chloroform, washed with sodium carbonate solution, freed from solvent, and then distilled under 10 mm. pressure.

Cut 2, b.p. up to 125°, 5.8 g. of light yellow oil which became reddish-brown overnight. The residue was 12.3 g. of viscous oil.

The distillates were combined and fractionated under 9 mm. pressure using a 12-cm. Vigreux column. The cuts boiling up to 76° (3.8 g.) contained considerable methyl benzoate (carried over from the preparation of the peroxy acid). The remaining volatile material came over between 77° and 87° (3.0 g.) at bath temperatures up to 175°. It had n_D^{25} 1.455. All the cuts were sparingly water-soluble. The distillation residue was 5 g. of viscous reddish-brown oil.

The distillates could be hydrolyzed by heating with 1 N hydrochloric acid to a reducing, water-soluble oil which when heated with a solution of 2,4-dinitrophenylhydrazine hydrochloride gave the *2,4-dinitrophenylosazone* of *3,4-didesoxyaldopentose*, m.p. 242°.

The two distillation residues were hydrolyzed by fifteen minutes' heating on the steam-bath with 1 N hydrochloric acid, the solution neutralized and the water distilled under reduced pressure. The product was 12.9 g. of an ether-soluble oil. This gave the 2,4-dinitrophenylosazone of 3,4-didesoxypentose under the usual conditions. When it was acetylated using acetic anhydride and pyridine and the product distilled, 9.5 g. of acetate (b.p. 70–78° under less than 1 mm. pressure; n_D^{25} 1.444) was obtained. This corresponds in properties with the *diacetate* of *3,4-didesoxyaldopentose* and was hydrolyzed to a reducing substance which gave the 2,4-dinitrophenylosazone of the aldose.

Pyrolysis of glucose. These are general directions for the several experiments. The glucose sample (alone or mixed with crushed glass) was placed in a 200-cc. round-bottom flask and weighed. The air in the flask was replaced by nitrogen, the flask evacuated and then immersed in a bath at the desired temperature. At the end of the heating period, the flask and its contents were cooled and dry air introduced. The loss in weight was determined. If the resulting glassy product was to be extracted with dry methanol, it was broken up as well as possible under that solvent.

For the dioxane extractions the product was heated to near the boiling point of dioxane

in the presence of the dry solvent. The glassy product was soft at that temperature and therefore could be worked mechanically to aid contact with the solvent. The dioxane solution was decanted, cooled, and the bulk of the solvent removed under reduced pressure. The semisolid which separated was filtered in a stream of dry air.

Propionylation and *acetylation* were carried out by dissolving the material in up to ten times its weight of dry pyridine, adding ten times its weight of acid anhydride with cooling to keep the temperature near 30°, then allowing the mixture to stand at room temperature for fifteen to twenty hours.

Deacetylations were effected by treatment of the esters with a little sodium methoxide in a large excess of dry methanol at 0°. After a period of four hours the base was neutralized with acetic acid and then the methanol and methyl ester removed under diminished pressure.

Selected runs are collected in Table II.

Distillation of propionates. The propionate of the methanol-soluble fractions (29 g.) from runs 1, 2, and 4 in Table I was distilled at 10^{-5} to 10^{-3} mm. (A) Bath temperature 185–190°; 3.4 g.; $[\alpha]_D$ +23.9° (*c*, 1.05 in methanol); Mol. wt., 410; propionyl content 59.5%. (B) Bath temperature 210–225°; 6.6 g.; $[\alpha]_D$ +32° (*c*, 1.48 in methanol); Mol. wt., 412; propionyl content 61.3%. (C) Bath temperature up to 265°; 1.7 g.; $[\alpha]_D$ +31° (*c*, 1.27 in methanol); Mol. wt., 430; propionyl content 60.0%. (D) Bath temperature 265°; 3.0 g.; $[\alpha]_D$ +43.5° (*c*, 1.30 in methanol); Mol. wt., 540; propionyl content 55.5%.

The molecular weights were determined cryoscopically in benzene. From values for knowns it is probable that the above values are 5–10% low.

The propionyl determinations were made by the method of Kunz and Hudson (15). The above values are corrected for a consistent error of +1% found with glucose pentapropionate when the ester stood for three hours at −10° in the presence of the base.

An attempt was made to distill the residue from this distillation in a simple molecular still. In four hours at 200° under 10^{-5} mm. a negligible quantity distilled. When cuts 1, 2, and 3 were depropionylated, the products consisted of glucose and amorphous residues which gave considerable glucose acetates on acetylation. Cut 4 gave no crystalline sugar or acetate.

Acid hydrolysis. A solution of 2.5 g. of the methanol-soluble product from runs 1, 2, and 4 in 8 cc. of 0.3 *N* hydrochloric acid was heated on the steam-bath for forty minutes, the final volume being 4 cc. After the addition of 15 cc. of ethanol and neutralization of the acid with sodium carbonate, the solution was filtered from precipitated salt and colored gum. After removal of 0.3 g. of the complex of glucose and sodium chloride which slowly crystallized, the solvent was removed from the solution under reduced pressure. The residue was acetylated with acetic anhydride in pyridine. A small quantity of β-D-glucose pentaacetate was obtained from a methanol solution of the 3.1 g. of product. The remaining 2.8 g., after removal of the methanol, was dissolved in benzene and put through a 2.5 × 29.5-cm. column of 5:1 Magnesol-Celite mixture previously wet with benzene. The chromatogram was developed using benzene–ethanol solutions changing in ethanol content from a 100–1 to a 1–1 ratio. The eluate contained no ester. The column was sectioned and found to contain the bulk of the material between the 18 and 26 cm. depths, half of it in a 2.5-cm. range. The *acetate* ranged in molecular weight from 530 at the top to 440 at the bottom of the absorbed material (Calc'd for monosaccharide pentaacetate, 390; an anhydrodisaccharide hexaacetate, 576). None of the acetates from the various segments could be crystallized.

Action of methanol and hydrochloric acid. Methanol-soluble material from runs 1, 2, and 4 (0.58 g.) was dissolved in 15 cc. of dry methanol and hydrogen chloride was bubbled through the solution for two minutes. The solution was heated on the steam-bath for fifteen minutes, neutralized with solid sodium carbonate, treated with activated charcoal, and filtered. After concentration to a volume of 3 cc. and seeding, 0.2 g. of methyl α-D-glucoside crystallized. Fifty mg. of methyl β-D-glucoside crystallized slowly from the mother liquor. The remaining material could not be crystallized.

Sodium chloride diglucose. The 0.3 g. of crystals mentioned above was crystallized

TABLE II

Pyrolysis of d-Glucose

α-D-GLUCOSE G.	PRESSURE MM.	TEMP., °C.	TIME MIN.	LOSS OF WATER g.	LOSS OF WATER mole %	REMARKS
20.0	22	157–163	230	1.8	90	Product 60% soluble in dry methanol. Benzoate of soluble material could not be crystallized.
10.0	15	150–155	330	1.0	100	Product 80% soluble in methanol. No crystalline solid obtained.
20.0	1	151–155	150	0.7	35	Recovered 7% of the glucose unchanged. Less than 1 g. extracted by 60 cc. of boiling dry dioxane. Amorphous, and gave glucose acetates.
25.2	1	165	165	1.3	55	Propionate 50% distilled. Distillate Mol wt., 430. Residue Mol wt., 820.
11	1	150–160	285	1.5	140	Product 30% soluble in dry methanol.
12	1	148–154	150	0.8	66	Crushed soft glass added. Product completely soluble in dry methanol; 20% of the glucose recovered.
26.0	1	153–157	150	2.1	80	Crushed soft glass. Propionate 40% distillable. Distillate Mol wt., 430. Residue Mol wt., 930.
21.0	1	160	150	2.4	110	Crushed soft glass. Two 50-cc. portions of hot dry dioxane dissolved 2 g. of amorphous solid. This gave glucose esters.
20.0	3	163–167	135	1.3	65	Crushed soft glass. Propionate 50% distillable. Distillate Mol. wt., 440. Residue Mol. wt., 890.
21.2	1	163–167	150	2.2	100	Crushed pyrex glass. Propionate 25% distillable. Distillate Mol. wt., 425. Residue Mol. wt., 1020.
β-D-GLUCOSE, G. 14	1	160	150	1.0	70	Amorphous product. Only a trace of dioxane-soluble material. No glucose recoverable.

thrice from dry methanol. When immersed in a bath at 140° and heated, the crystals softened at 164° and melted at 168°. The compound gave an ash when burned, reacted instantly with aqueous silver nitrate to form silver chloride, and gave a mixture of glucose

pentaacetates when treated with acetic anhydride and pyridine. Specific rotation, $[\alpha]_D$ (*c*, 1.534 in water) changed from 77.6° to 46.2°.

Anal. Calc'd for $C_{12}H_{24}ClNaO_{12}$: C, 34.4; H, 5.74.
Found: C, 34.49; H, 5.68.

Acknowledgment. Combustion analyses for carbon, hydrogen, and nitrogen were performed by P. Craig, J. Gibbs, M. Hines, and V. Hobbs.

SUMMARY

The literature on crystalline α-glucosan has been critically reviewed. The thermal dehydration of α- and β-D-glucose under reduced pressure has been found to give predominantly materials of higher molecular weight. No evidence for the formation of α-glucosan was found.

The anhydrous crystalline complex of glucose and sodium chloride, $(C_6H_{12}O_6)_2 \cdot NaCl$, was described.

Pyrolysis of 3,4-didesoxyaldopentose has been shown to yield tetrahydrofurfural, 2,5-bis(trimethyleneoxy)-1,4-dioxane, a crystalline isomer of the latter, and water-soluble materials of higher molecular weight. Mechanisms were suggested for the formation of the products.

Derivatives of 3,4-didesoxyketopentose were described. New derivatives of tetrahydrofurfural were included also.

The action of peroxybenzoic acid on dihydropyran was shown to give crude 2,3-epoxytetrahydropyran and higher molecular weight products which could be hydrolyzed in part to tetrahydropyran-2,3-diol.

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[Contribution from the Quaker Oats Company Research Laboratories]

BY-PRODUCTS FROM HYDROGENATION OF FURFURYL ALCOHOL

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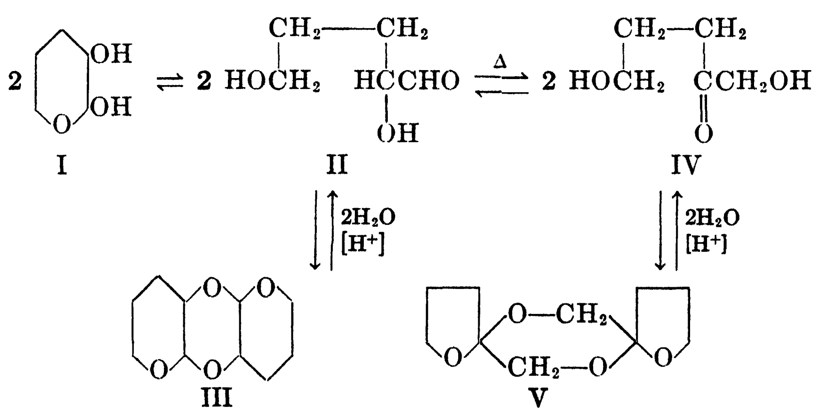
The commercial production of tetrahydrofurfuryl alcohol by the hydrogenation of furfuryl alcohol over Raney nickel results in the formation of a number of by-products. In practice, these are separated by fractional distillation, being recovered as a low-boiling fore-run and a high-boiling residue. From these fractions it has been possible to isolate and identify all of the compounds attributable to hydrogenolysis (1) or hydrolytic ring cleavage (2). However, these side reactions do not account for all of the by-products, and it is the object of this paper to discuss yet another type of reaction which may contribute to the complexity of the hydrogenation process.

On careful fractional distillation of the high-boiling residue, a small quantity of a white, crystalline solid was observed to separate from the fraction boiling in the range of the 1,5-pentanediol component. Recrystallization showed it to be a pure compound, $C_{10}H_{16}O_4$, which had not been previously described. Tests for carboxyl, hydroxyl, carbonyl, and ester groups gave negative results, and there was no evidence for unsaturation. Following a mild acid hydrolysis, positive tests were obtained for hydroxyl and carbonyl, and it was possible to prepare both a hydrazone and an osazone. Results of the analysis of these two derivatives could be explained if the hydrazone and osazone were assumed to be the corresponding derivatives of an oxopentanediol, in which one of the hydroxyl groups is alpha to the carbonyl. Assuming that the oxopentanediol was II or IV, we postulated formula III or V to account for the experimental findings of our white, crystalline solid. Mild acid hydrolysis would be expected to split such tricyclic diacetals into two molecules of II or IV.



During a discussion shortly thereafter, Prof. C. D. Hurd disclosed to us that he and Mr. O. E. Edwards had, in the course of their work, isolated a compound which behaved surprisingly similar to our crystalline solid. A mixed melting

point determination confirmed their identity. Hurd and Edwards (3) have now reported their compound which was obtained by thermal dehydration of 2,3-dihydroxytetrahydropyran (3,4-didesoxyaldopentose), I, which is the cyclic form of 2,5-dihydroxyvaleraldehyde, II. However, they propose 2,5-bis(trimethyleneoxy)-1,4-dioxane, V, and not III, as the structure of their crystalline solid,[1] and the mechanism of its formation from I as proceeding *via* the isomeric compounds II and IV. This follows from the fact that a keto- rather than an aldopentose is formed on mild hydrolysis of the crystalline compound. While the osazone of the hydrolysate is identical with that obtained from I, the hydrazones from these sources are not identical, but isomeric (3).

While the mechanism indicated above explains the formation of the new compound, V, from I, it does not explain the occurrence of V in the products of hydrogenation of furfuryl alcohol. Under the conditions of the latter process, the formation of any of the precursors of V (I, II or IV) is considered to be extremely unlikely. However, if one were to interpose certain intermediate steps in the conversion of IV into V, a relationship of the origin of V from thermal dehydration of IV and from hydrogenation of furfuryl alcohol, VI, can be shown. If we postulate 4,5-dihydrofurfuryl alcohol, VII, (through dehydration of IVa, the cyclic form of IV) as an intermediate in the formation of V from IV, we can account for the occurrence of the same intermediate during the hydrogenation process. Schniepp and others (5, 6) have shown that methylfuran can undergo 4,5-dihydrogenation and that this is probably an intermediate in the complete hydrogenation to methyltetrahydrofuran. If we assume a similar course in the hydrogenation of furfuryl alcohol, the resulting intermediate would be 4,5-dihydrofurfuryl alcohol, VII.

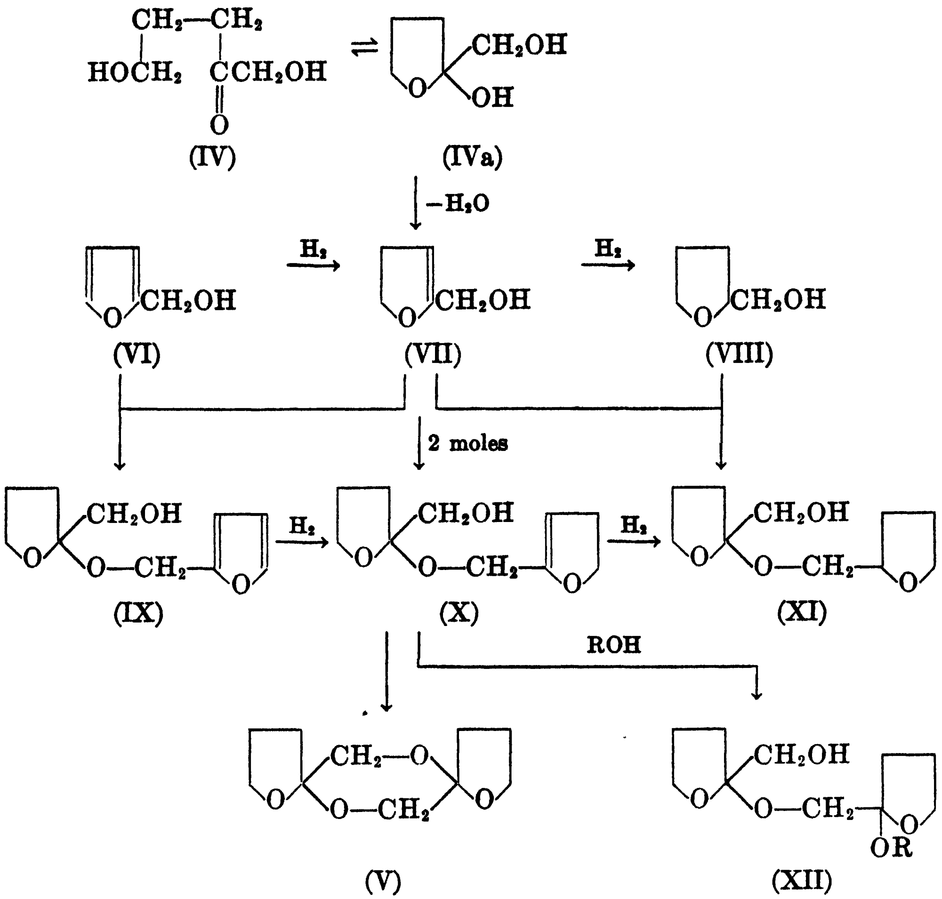
As a vinyl ether possessing a primary hydroxyl group, VII might be expected to dimerize to X, and this on intramolecular addition of the hydroxyl group across the remaining double bond would result in the formation of the new compound, V. Addition of VI to VII might also give V by way of IX and X as illustrated.

This suggested mechanism may also account for a number of the as yet unidentified by-products in the high-boiling residue obtained in the manufacture of furfuryl alcohol. Thus, any of the hydroxylic compounds present in the reaction mixture[2] is capable of adding across the reactive double bond of either VII or X to give individual new compounds. Some of these possibilities are shown in the above diagram (VII + VIII = XI and X + ROH = XII). Furthermore, hydrogenolysis and/or hydrolysis of any of these compounds would give rise to yet additional by-products. It will be of interest to reexamine the high-boiling residue in the light of these considerations.

In a similar manner, it is possible to explain the observation of Adkins (1) of

[1] Among other products they obtained were tetrahydrofurfural, and a higher-melting crystalline solid which may have the structure III.

[2] These are quite numerous, and include not only the saturated and unsaturated furan alcohols, but also a variety of pentanols (*e.g.* 1-ol, 2-ol, 1,2-diol, 1,4-diol, 1,5-diol, and 1,2,5-triol).



the occurrence of 1,9-dioxa-5-spirononane as a product of the hydrogenation of furylacrolein over Raney nickel. 4,5-Dihydrogenation of either the furylpropanol or furylpropenol intermediate, and subsequent intramolecular addition of the hydroxyl group across the double bond of the vinyl ether so formed, would produce the spirane.

EXPERIMENTAL

2,5-Bis(trimethyleneoxy)-1,4-dioxane (*V*). Fractional distillation of a 3.78-liter sample of high-boiling residue from commercial tetrahydrofurfuryl alcohol manufacture (hydrogenation of furfuryl alcohol over Raney nickel) gave 517 grams of a fraction boiling in the range of 1,5-pentandiol (130–131°/11 mm.). The solid phase was filtered off and washed with ether; yield, 118 grams, approximately 3% of the residue sample, or 0.8% of the original crude hydrogenation product. The solid was recrystallized four times from ether before a constant melting sample (101.4–101.8° using an Anschütz thermometer) was obtained. Hurd and Edwards (3) report 103° as the melting point of their sample of V and found no depression in melting point[3] when mixed with a sample of our compound.

Anal. Calc'd for $C_{10}H_{16}O_4$: C, 59.99; H, 8.06; Mol. wt., 200.

Found: C, 59.84; H, 8.09; Mol. wt. (cryoscopically in benzene), 200.

[3] Private communication.

1,5-Dihydroxy-4-pentanone (IV). This compound was not isolated as such but its osazone and hydrazone derivatives were prepared.

2,4-Dinitrophenylosazone of IV. Refluxing 0.2 g. of V, 0.4 g. of 2,4-dinitrophenylhydrazine, 0.5 ml. of conc'd HCl, and 25 ml. of ethanol for 15 minutes, cooling and recrystallizing the precipitate from nitrobenzene gave the osazone melting at 235–236° with decomposition [reported (4) as 242°].

Anal. Calc'd for $C_{17}H_{16}N_8O_9$: C, 42.86; H, 3.39; N, 23.53.
Found: C, 44.13; H, 3.33; N, 23.11.

2,4-Dinitrophenylhydrazone of IV. A solution of 0.2 g. of V. in 5 ml. of 0.1 *N* HCl was warmed for 15 minutes after which 0.4 g. of 2,4-dinitrophenylhydrazine and 25 ml. ethanol were added and the mixture boiled under reflux for 15 minutes. On cooling, the solution was filtered and an equal volume of water added to the filtrate. The hydrazone was recrystallized by solution in ethanol followed by dilution with water. The melting point was 155–155.5° [reported (3) as 164–165°, when immersed at 140°].

Anal. Calc'd for $C_{11}H_{14}N_4O_6$: C, 44.29; H, 4.73; N, 18.79.
Found: C, 45.01; H, 4.77; N, 18.57.

SUMMARY

A component of the by-products from the hydrogenation of furfuryl alcohol to tetrahydrofurfuryl alcohol has been identified as 2,5-bis(trimethyleneoxy)-1,4-dioxane and is identical with one of the compounds obtained by Hurd and Edwards on pyrolysis of 3,4-didesoxyaldopentose.

A mechanism is proposed for the formation of the compound during the hydrogenation of furfuryl alcohol. The mechanism may also account for a number of the as yet unaccounted for components of the by-products.

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[Contribution from the Central Research Department, Monsanto Chemical Company]

ALKOXYCHLOROALKENES

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Straus and Thiel (1) showed that in the presence of mercuric chloride methyl α-chlorobenzyl ether added to butadiene to give 65% of 1-phenyl-1-methoxy-5-chloro-3-pentene and that in the presence of zinc chloride, methyl chloromethyl ether added to butadiene to give 70% of a mixture of 5-methoxy-3-chloro-1-pentene and 5-methoxy-1-chloro-2-pentene. For the latter reaction stannic chloride was as good a catalyst as zinc chloride, antimony pentachloride much better, and mercuric chloride poorer. The same type of addition was effected with methyl α-bromobenzyl ether and with bromomethyl ether.

We have found this reaction to be general for butadiene and α-chloroethers. We have effected the addition of twelve α-chloroethers to butadiene in the presence of zinc chloride and in each case have obtained a mixture of the 5-alkoxy-3-chloro-1-alkene and the 5-alkoxy-1-chloro-2-alkene in yields of 61–86%. The isomers were separated by fractional distillation at reduced pressure, since they isomerized when heated at atmospheric pressure.

$$\mathrm{ROCHClR'} + \mathrm{CH_2{=}CHCH{=}CH_2} \xrightarrow{\mathrm{ZnCl_2}} \mathrm{R'}\underset{\substack{|\\ \mathrm{OR}}}{\mathrm{C}}\mathrm{HCH_2CHClCH{=}CH_2} + \mathrm{R'}\underset{\substack{|\\ \mathrm{OR}}}{\mathrm{C}}\mathrm{HCH_2CH{=}CHCH_2Cl}$$

As shown in Table I the higher-boiling isomer has been postulated as the 1,4-adduct. This postulation is based on boiling point and on the fact that the alcohols (predominantly primary) prepared therefrom are much more readily esterified than those (largely secondary) prepared from the lower boiling isomers.

In the presence of zinc chloride either of these compounds rearranges into a mixture of the two isomers (2).

Treatment of seven of these chlorides with boiling aqueous sodium carbonate gave unsaturated alcohols in 52–91% yields. In some cases both isomers were isolated. Since these hydrolyses were conducted in aqueous emulsion, this probably was a rearrangement of the intermediate carbonium ion before it could add

$$\mathrm{R}\underset{\substack{|\\ \mathrm{Cl}}}{\mathrm{C}}\mathrm{HCH{=}CH_2} \xrightarrow{\mathrm{Na_2CO_3}} \mathrm{R}\overset{+}{\mathrm{C}}\mathrm{HCH{=}CH_2} \rightleftharpoons \mathrm{RCH{=}CH}\overset{+}{\mathrm{C}}\mathrm{H_2}$$

$$\downarrow \mathrm{OH^-} \qquad\qquad \downarrow \mathrm{OH^-}$$

$$\mathrm{R}\underset{\substack{|\\ \mathrm{OH}}}{\mathrm{C}}\mathrm{HCH{=}CH_2} \qquad \mathrm{RCH{=}CHCH_2OH}$$

an hydroxyl ion. At the temperature employed (100°) neither the chlorides nor the alcohols rearrange by themselves. Hydrogenation of nine of the unsaturated alcohols in ethanol solution in the presence of Raney nickel gave the corresponding saturated alcohols in 73–92% yields.

TABLE I

ALKOXYCHLOROPENTENES AND ALKOXYCHLOROHEXENES

COMPOUND	B.P., °C./MM.	n_D^{25}	d_{25}^{25}	% YIELD	CALC'D C	CALC'D H	FOUND C	FOUND H
5-Methoxy-3-chloro-1-pentene[a]	49/19	1.4345(20°)	0.973($^{20}_{20}$)	66	53.5	8.18	54.3	8.05
5-Methoxy-1-chloro-2-pentene[b]	71/20	1.4512	.998		53.5	8.18	54.2	8.05
5-Ethoxy-3-chloro-1-pentene	65/21	1.4370	.959	61	56.6	8.75	56.6	8.96
5-Ethoxy-1-chloro-2-pentene	77/19	1.4460	.971		56.6	8.75	57.3	9.03
5-*n*-Propoxy-3-chloro-1-pentene	77.5/19	1.4380	.946	85	59.0	9.22	59.3	9.30
5-*n*-Propoxy-1-chloro-2-pentene	90/19	1.4445	.951		59.0	9.22	59.7	9.11
5-*n*-Butoxy-3-chloro-1-pentene	60/1	1.4400	.931	77	61.2	9.62	62.0	9.72
5-*n*-Butoxy-1-chloro-2-pentene	74/1	1.4485	.943		61.2	9.62	62.4	9.66
5-*n*-Pentyloxy-3-chloro-1-pentene	70.5–71.0/2	1.4367	.908	77	63.0	10.0	64.0	10.4
5-*n*-Pentyloxy-1-chloro-2-pentene	85/2	1.4517	.937		63.0	10.0	62.8	10.0
5-(3-Methylbutoxy)-3-chloro-1-pentene	92/3	1.4440	.929	84.3	62.9	9.99	63.4	9.79
5-(3-Methylbutoxy)-1-chloro-2-pentene	109/5	1.4485	.935		62.9	9.99	63.8	9.97
5-(2-Ethylhexoxy)-3-chloro-1-pentene	93/1	1.4478	.912	76	67.0	10.75	67.5	10.75
5-(2-Ethylhexoxy)-1-chloro-2-pentene	108/1(dec.)	1.4467	.896		67.0	10.75	—	—
5-Cyclohexoxy-3-chloro-1-pentene	85/3	1.4700	.986	77.5	65.4	9.40	67.2	9.85
5-Cyclohexoxy-1-chloro-2-pentene	90/3	1.4725	.987		65.4	9.40	66.6	9.63
5-(2-Chloroethoxy)-3-chloro-1-pentene	75/2	1.4660	1.128	82	45.9	6.56	45.6	6.60
5-(2-Chloroethoxy)-1-chloro-2-pentene	84/2	1.4735	1.130		45.9	6.56	46.1	6.60
5-Ethoxy-3-chloro-1-hexene	62/16	1.4315	0.921	86	59.0	9.2	59.1	9.5
5-Ethoxy-1-chloro-2-hexene	77.5–78.5/14	1.4489	.964		59.0	9.2	59.0	9.2
5-*n*-Butoxy-3-chloro-1-hexene	67.5/3	1.4386	.917	75	63.0	10.0	63.0	10.1
5-*n*-Butoxy-1-chloro-2-hexene	83/3	1.4490	.931		63.0	10.0	63.2	10.1
5-Isobutoxy-3-chloro-1-hexene	44/1	1.4321	.900	66	63.0	10.0	63.5	10.3
5-Isobutoxy-1-chloro-2-hexene	56/1	1.4449	.922		63.0	10.0	63.1	9.7

[a] Pudovik (2) gives b.p. 34–35°/11 mm., n_D^{20} 1.4364, d_4^{20} 0.969.

[b] Pudovik (2) gives b.p. 58–59°/13 mm., n_D^{20} 1.4540, d_4^{20} 1.001.

5-*n*-Butoxy-1-chloro-2-pentene reacted with sodium acetate in boiling acetamide to give 5-*n*-butoxy-2-penten-1-yl acetate in 73% conversion and 88% yield. In boiling glacial acetic acid the conversion was 64% and the yield 77%. With sodium acetate in acetic acid solution 5-isobutoxy-1-chloro-2-hexene gave the acetate in 58% yield, which was hydrogenated in the presence of Raney nickel to give 75% of 5-isobutoxy-1-hexyl acetate.

When 5-*n*-butoxy-1-chloro-2-pentene and sodium adipate were heated at 160–170° in the presence of triethylamine, a 61% yield of 5-*n*-butoxy-2-penten-1-yl adipate was obtained. Hydrogenation in the presence of Raney nickel gave 32% of the corresponding saturated adipate.

Five other saturated esters of dibasic acids were prepared by heating the corresponding alcohol and dibasic acid (or its anhydride) while the evolved water was removed as its azeotrope with toluene. The yields were 72–92%. 5-Isobutoxy-1-hexyl 4-ketopimelate was prepared in 49% yield by transesterification of the ethyl ester in the presence of a *p*-toluenesulfonic acid catalyst.

5-Ethoxy-3-chloro-1-pentene, 5-ethoxy-1-chloro-2-pentene, the mixture of 5-*n*-butoxy-3-chloro-1-pentene and 5-*n*-butoxy-1-chloro-2-pentene, and the mixture of 5-isobutoxy-3-chloro-1-hexene and 5-isobutoxy-1-chloro-2-hexene all reacted with *n*-butylamine to give 65–78% of the corresponding secondary amines. Hydrogenation in the presence of Raney nickel of *n*-butyl-5-ethoxy-2-pentenyl-1-amine, the mixed *n*-butyl-*n*-butoxypentenylamines, and the mixed *n*-butyl-isobutoxyhexenylamines gave the corresponding saturated secondary amines. The benzamide of the *n*-butyl-*n*-butoxypentylamines and the benzenesulfonamide of the *n*-butyl-isobutoxyhexylamines were prepared by the Schotten-Bauman method.

5-Methoxy-1-chloro-2-pentene, 5-methoxy-3-chloro-1-pentene, 5-*n*-butoxy-1-chloro-2-pentene, and 5-*n*-butoxy-3-chloro-1-pentene reacted with ammonium thiocyanate in boiling ethanol to give isothiocyanates in 58–86% yield. Since in each case the low-boiling chloride gave the high-boiling isothiocyanate, predominately, and *vice versa*, an allylic type rearrangement probably was involved. All

$$CH_3OCH_2CH_2CHClCH{=}CH_2 \xrightarrow{NH_4SCN} \left[CH_3OCH_2CH_2\underset{\displaystyle SCN}{\underset{|}{C}}HCH{=}CH_2 \right]$$

$$\longrightarrow CH_3OCH_2CH_2CH{=}CHCH_2NCS$$

four products gave a strong test for the isothiocyanate group and a negative test for the thiocyanate group. Both crotyl thiocyanate and β-ethylallyl thiocyanate undergo such a rearrangement on distillation (3). Mumm and Richter postulated a cyclic intermediate for this particular allyl rearrangement.

α-Chloroethers. The chloromethyl ethers were prepared by the method described for monochloromethyl ether (4). *n*-Butyl and *n*-pentyl chloromethyl ethers also were pre-

[1] All analyses are microanalyses performed by the Oakwold Laboratories, Alexandria, Virginia and the Micro-Tech Laboratories, 800 Lincoln Ave., Skokie, Illinois.

pared in 87–90% yields by saturating a cold solution of trioxane in the appropriate alcohol with hydrogen chloride (5). The α-chloroethyl ethers were prepared by a modification of the Reppe and Baur synthesis (6). The vinyl ether was added to a saturated solution of hydrogen chloride in the reaction product.

Alkoxychloropentenes and alkoxychlorohexenes. A mixture of five moles of the appropriate α-chloroalkyl ether and 20 g. of fused zinc chloride was placed in a 1-liter, three-necked flask equipped with a rubber-sealed stirrer, thermometer, and gas inlet tube. Butadiene was introduced into the mixture while the temperature was held at 0–20°. When the solution was saturated, the stirring was continued while aqueous sodium carbonate was introduced to wash out the catalyst and destroy any excess chloroether. The layers were separated and the organic portion, diluted with benzene, was washed several times with water, dried over Drierite, and distilled. In each case the 5-alkoxy-3-chloro-1-pentene and the 5-alkoxy-1-chloro-2-pentene were separated by careful fractional distillation. The properties of these compounds are summarized in Table I.

Alkoxypentenols and alkoxyhexenols. A typical preparation is that of 5-*n*-butoxy-1-hexen-3-ol and 5-*n*-butoxy-2-hexen-1-ol.

A mixture of 130 g. of sodium carbonate, 1250 cc. of water, and 190.5 g. of mixed *n*-butoxychlorohexenes was heated with stirring at 100° for seventeen and one-half hours. Upon cooling, the reaction mixture was twice extracted with 200-cc. portions of benzene. Distillation of the combined extracts yielded 154 g. (89%) of mixed *n*-butoxyhexenols, b.p. 110–138°/19 mm.

In other experiments acetone, activated copper powder or a wetting agent was added, without appreciably improving the yield. The properties of the compounds prepared are shown in Table II.

In some of these hydrolyses both isomeric alkenols were isolated. In the 5-*n*-pentyloxy-1-chloro-2-pentene hydrolysis the 126 g. (91%) of crude product was carefully distilled through a Lecky-Ewell column to give 26 g. (19%) of 5-*n*-pentyloxy-1-penten-3-ol, b.p. 116–122°/20 mm.; 12 g. (9%) of intermediate, b.p. 122–142°/20 mm.; and 66 g. (48%) of 5-*n*-pentyloxy-2-penten-1-ol, b.p. 142–143°/20 mm. With 5-ethoxy-3-chloro-1-hexene considerably more rearrangement occurred. Distillation of the 132 g. (91%) of crude product yielded 28 g. (19%) of 5-ethoxy-1-hexen-3-ol, b.p. 80–83°/14 mm., n_D^{25} 1.4320–1.4318; 7 g. (5%) of intermediate, b.p. 83–107°/14–15 mm.; and 69 g. (48%) of 5-ethoxy-2-hexen-1-ol b.p. 107–110°/15 mm., n_D^{25} 1.4467–1.4457. The 12 g. residue, n_D^{25} 1.4460, represented an additional 8% of 5-ethoxy-2-hexen-1-ol. In the 5-ethoxy-1-chloro-2-hexene hydrolysis the 117 g. (86%) of crude product was separated into 11 g. (8%) of 5-ethoxy-1-hexen-3-ol, b.p. 83–85°/20 mm.; 5 g. (4%) of intermediate, b.p. 85°/20 mm.–98°/12 mm.; and 77 g. (56%) of 5-ethoxy-2-hexen-1-ol, b.p. 98–103°/12 mm. In the hydrolysis of 232 g. of 5-*n*-butoxy-1-chloro-2-pentene the product consisted of 42 g. (20%) of 5-*n*-butoxy-1-penten-3-ol, b.p. 99–104°/13 mm., n_D^{25} 1.4408; 8 g. (4%) of intermediate; and 126 g. (61%) of 5-*n*-butoxy-2-penten-1-ol, b.p. 123–125°/13 mm., n_D^{25} 1.4483. With 5-*n*-butoxy-3-chloro-1-pentene the results were similar. From 188 g. of the chloro compound were obtained 54.5 g. (32%) of 5-*n*-butoxy-1-penten-3-ol, b.p. 98–103.5°/13 mm., n_D^{25} 1.4395–1.4375; 6 g. (4%) of intermediate, b.p. 103.5–123°/13 mm.; and 77 g. (46%) of 5-*n*-butoxy-2-penten-1-ol, b.p. 123–125°/13 mm., n_D^{25} 1.4479.

Alkoxypentanols and alkoxyhexanols. These compounds were prepared by hydrogenating the corresponding alkoxypentenols and alkoxyhexenols at 75–100° in the presence of 10% of Raney nickel and at about 1000 lbs. hydrogen pressure. The unsaturated alcohol always was diluted with an equal volume of ethanol. The properties of these compounds are summarized in Table II.

Esters. A few esters were prepared by treating the unsaturated chlorides with the sodium salts of the corresponding acids. These reactions are described in detail below.

5-n-Butoxy-2-penten-1-yl acetate. A mixture of 116 g. of acetamide, 31 g. of sodium acetate, and 59 g. of 5-*n*-butoxy-1-chloro-2-pentene was boiled under reflux for two and onehal hours. Upon cooling, the product was treated with 200 cc. of water and the aqueous

TABLE II

ALKOXYALKENOLS AND ALKOXYALKANOLS

COMPOUND	B.P., °C/MM.	n_D^{25}	d_{25}^{25}	% YIELD	CALC'D		FOUND	
					C	H	C	H
5-Methoxy-2-penten-1-ol	96–98/19	1.4480	0.966	52	62.1	10.3	62.2	10.7
5-*n*-Butoxy-1-penten-3-ol	98–99/14	1.4375	0.894	85	68.4	11.4	68.5	11.1
5-*n*-Butoxy-2-penten-1-ol	121–122/13	1.4466	0.909		68.4	11.4	67.9	12.0
5-*n*-Pentyloxy-1-penten-3-ol	120–121/20	1.4426	0.905	91	69.8	11.6	68.0	11.2
5-*n*-Pentyloxy-2-penten-1-ol	143/20	1.4498	0.901		69.8	11.6	68.8	11.5
5-Ethoxy-1-hexen-3-ol	82–83/14	1.4318	0.896	91	66.7	11.1	66.8	11.1
5-Ethoxy-2-hexen-1-ol	101–103/12	1.4477	0.923		66.7	11.1	65.6	11.2
n-Butoxyhexenols	110–138/19			89				
Isobutoxyhexenols	90–95/2.5	1.4414		72	69.8	11.6	69.6	11.6
5-Isobutoxy-2-hexen-1-ol	106/2.6–90/1.5	1.4435	0.899	70	69.8	11.6	68.7	11.3
1-*n*-Butoxy-3-pentanol	98–99/14	1.4290	0.891	—	67.5	12.5	66.7	12.5
5-*n*-Butoxy-1-pentanol	90–94/2	1.4334	0.891	92	67.5	12.5	67.6	12.7
5-*n*-Pentyloxy-1-pentanol	139–141/20	1.4357	0.884	87	69.1	12.7	68.2	12.8
2-Ethoxy-4-hexanol	79–80/15	1.4190	0.879	—	65.8	12.3	65.8	12.6
5-Ethoxy-1-hexanol	99–101/12	1.4318	0.903	87	65.8	12.3	64.8	12.4
2-*n*-Butoxy-4-hexanol	103.5–104.5/15	1.4270	0.870	—	69.1	12.7	69.3	13.2
5-*n*-Butoxy-1-hexanol	127.5/15	1.4335	0.882	—	69.1	12.7	68.9	12.8
2-Isobutoxy-4-hexanol	98–99/14	1.4317	0.895	—	69.0	12.6	68.5	12.7
5-Isobutoxy-1-hexanol	120–121/15	1.4305	0.875	73	69.0	12.6	68.9	12.6

layer separated. The organic portion was diluted with 120 cc. of ether and then washed twice with 4% hydrochloric acid and twice with water. After the ether had been distilled, there was obtained 6 g. (10% recovery) of 5-*n*-butoxy-1-chloro-2-pentene, b.p. to 92°/2.3 mm. and 49 g. (73% conversion and 88% yield) of 5-*n*-butoxy-2-penten-1-yl acetate, b.p. 92–97°/2.3 mm., n_D^{25} 1.4390. An analytical sample boiled at 96–97°/2.3 mm., n_D^{25} 1.4392, d_{25}^{25} 0.937.

Anal. Calc'd for $C_{11}H_{20}O_3$: C, 66.0; H, 10.0
Found: C, 66.2; H, 10.1.

When 5-*n*-butoxy-1-chloro-2-pentene and sodium acetate were boiled for eight hours in glacial acetic acid solution, 5-*n*-butoxy-2-penten-1-yl acetate was obtained in 64% conversion and 77% yield.

5-Isobutoxy-2-hexen-1-yl acetate. A solution of 150 g. of sodium acetate and 191 g. of 5-isobutoxy-1-chloro-2-hexene in 425 g. of glacial acetic acid was boiled under reflux for seven hours. After cooling, the mixture was diluted with 200 cc. of water and extracted twice with benzene. The combined benzene extracts were washed once with water and distilled to give 125 g. (58%) of 5-isobutoxy-2-hexen-1-yl acetate, b.p. 92–94°/2 mm., n_D^{25} 1.4327.

Anal. Calc'd for $C_{12}H_{22}O_3$: C, 67.3; H, 10.3.
Found: C, 67.1; H, 10.1.

5-Isobutoxy-1-hexyl acetate. A 125-g. sample of 5-isobutoxy-2-hexen-1-yl acetate containing 5 g. of Raney nickel was shaken with hydrogen for three hours at 60° and 1000 lbs. pressure. After the nickel had been separated by filtration, the product was distilled to give 94 g. (75%) of 5-isobutoxy-1-hexyl acetate, b.p. 100–102°/4 mm., n_D^{25} 1.4210, d_{25}^{25} 0.901.

Anal. Calc'd for $C_{12}H_{24}O_3$: C, 66.7; H, 11.1.
Found: C, 66.5; H. 10.8.

5-n-Butoxy-2-penten-1-yl adipate was prepared by heating 176.5 g. of 5-*n*-butoxy-1-chloro-2-pentene with 96 g. of powdered sodium adipate for four hours at 160–170° in the presence of 3 cc. of triethylamine. After cooling, the mixture was diluted with a large excess of benzene and filtered. The filtrate was distilled at 0.7 mm. to a pot temperature of 200°. After it had been transferred to a Hickman still (7) the residue was distilled at 2×10^{-4}–10^{-5} mm. to give 130 g. (61%) of 5-*n*-butoxy-2-penten-1-yl adipate, n_D^{25} 1.4604, d_{25}^{25} 0.983.

Anal. Calc'd for $C_{24}H_{42}O_6$: C, 67.6; H, 9.85.
Found: C, 66.4; H, 10.2.

5-n-Butoxy-1-pentyl adipate was prepared by shaking 130 g. of 5-*n*-butoxy-2-penten-1-yl adipate and 25 g. of Raney nickel in 50 cc. of ethanol for seventy minutes with hydrogen at 90–110° and 800–1200 lbs. pressure. Upon cooling, the mixture was filtered free of catalyst and then distilled at 30 mm. to a pot temperature of 210°. The residue was taken up in ether and washed with aqueous sodium carbonate. After the ether was distilled, the 5-*n*-butoxy-1-pentyl adipate was distilled in a Hickman still at 10^{-4} mm. The yield was 42 g. (32%), n_D^{25} 1.4466, d_{25}^{25} 0.969.

Anal. Calc'd for $C_{24}H_{46}O_6$: C, 66.9; H, 10.7.
Found: C, 66.9; H, 11.1.

All but one of the remaining esters were prepared from the saturated alcohols and the corresponding acids. A typical example is the preparation of 5-*n*-butoxy-1-hexyl adipate shown below.

5-n-Butoxy-1-hexyl adipate. A mixture of 58 g. of 5-*n*-butoxy-1-hexanol, 25 g. of adipic acid, and 30 cc. of toluene was heated at 175–200° for fifteen and one-half hours while the evolved water was collected continuously in a Dean and Stark trap. Upon cooling, the reaction mixture was diluted with 200 cc. of benzene, washed with a solution of 10 g. of sodium hydroxide in 100 cc. of water and dried over potassium carbonate. Distillation yielded 61 g. (81%) of 5-*n*-butoxy-1-hexyl adipate, b.p. 214–218°/0.5 mm., n_D^{25} 1.4460, d_{25}^{25} 0.950.

Anal. Calc'd for $C_{26}H_{50}O_6$: C, 68.1; H, 10.9.
Found: C, 68.1; H, 11.7.

The 5-isobutoxy-1-hexyl 4-ketopimelate was prepared by transesterification of the ethyl ester in the presence of a *p*-toluenesulfonic acid catalyst.

The properties of all of these esters are summarized in Table III.

AMINES AND ISOTHIOCYANATES

n-Butyl-5-ethoxy-1-pentenyl-3-amine. A mixture of 149 g. of 5-ethoxy-3-chloro-1-pentene and 438 g. of *n*-butylamine was boiled under reflux for eight hours. Upon cooling, the product was shaken with a solution of 50 g. of sodium hydroxide in 250 cc. of water, the layers were separated and the organic portion was distilled to give 135 g. (72%) of *n*-butyl-5-ethoxy-1-pentenyl-3-amine, b.p. 92–115°/12 mm. An analytical sample boiled at 101°/15 mm., n_D^{25} 1.4341. d_{25}^{25} 0.837.

Anal. Calc'd for $C_{11}H_{23}NO$: Neut. equiv., 185; Found: Neut. equiv., 187.

n-Butyl-5-ethoxy-2-pentenyl-1-amine was prepared in the same way as the preceding amine. When the temperature reached 50°, the reaction became so vigorous that cooling was necessary. The yield of *n*-butyl-5-ethoxy-2-pentenyl-1-amine was 146 g. (78%), b.p. 106–116°/12 mm. An analytical sample boiled at 114–116°/12 mm., n_D^{25} 1.4434, d_{25}^{25} 0.846.

Anal. Calc'd for $C_{11}H_{23}NO$: Neut. equiv., 185; unsat. equiv., 185:

Found: Neut. equiv., 187; Unsat. equiv., 187[a].

n-Butyl-5-ethoxy-1-pentylamine. A small sample of *n*-butyl-5-ethoxy-2-pentenyl-1-amine was dissolved in ethanol and treated with hydrogen at 800 lbs. and 75° in the presence of Raney nickel. The pure *n*-butyl-5-ethoxy-1-pentylamine, obtained from this reaction, boiled at 130–131°/24 mm., n_D^{25} 1.4299, d_{25}^{25} 0.832.

Anal. Calc'd for $C_{11}H_{25}NO$: Neut. equiv., 187. Found: Neut. equiv., 189.

Mixed n-butyl-n-butoxypentylamines. A mixture of 438 g. of *n*-butylamine and 176.5 g. of 5-*n*-butoxy-1-chloro-2-pentene and 5-*n*-butoxy-3-chloro-1-pentene was warmed under reflux. When the reaction started, cooling was necessary. Subsequently the reaction was boiled under reflux for three and one-half hours. Upon cooling, the mixture was washed with a solution of 60 g. of sodium hydroxide in 350 cc. of water, then with a solution of 10 g. of sodium hydroxide in 50 cc. of water, and finally dried over potassium hydroxide. This crude product was shaken for five and one-half hours with hydrogen in the presence of 36 g. of Raney nickel at 160° and 1400–1500 lbs. pressure. After separating the catalyst, unreacted butylamine was distilled. The residue was washed with 100 cc. of 10% sodium hydroxide, dried over potassium hydroxide and distilled to give 101 g. of mixed *n*-butyl-*n*-butoxypentylamines, b.p. 92–98°/1 mm. An analytical sample boiled at 97–98°/1 mm.

Anal. Calc'd for $C_{13}H_{29}NO$: C, 72.5; H, 12.5.

Found: C, 72.4; H, 13.0.

Careful fractionation of the amine mixture gave *n*-butyl-1-*n*-butoxy-3-pentylamine, b.p. 125–128°/15 mm., n_D^{25} 1.4330, d_{25}^{25} 0.840,

Anal. Calc'd for $C_{13}H_{29}NO$: Neut. equiv., 217. Found: Neut. Equiv., 207.

and *n*-butyl-1-*n*-butoxy-5-pentylamine, b.p. 145°/15 mm., n_D^{25} 1.4339, d_{25}^{25} 0.832.

Anal. Calc'd for $C_{13}H_{29}NO$: Neut. equiv., 217. Found: Neut. Equiv., 216.

The *benzamide* was prepared by treating 39 g. of the mixed amines with 40 g. of sodium hydroxide in 200 cc. of water and with 50 cc. of benzoyl chloride according to the Schotten-Bauman method. The yield of amide was 33 g. (57%), b.p. 182–187°/2 mm., n_D^{25} 1.4980.

Anal. Calc'd for $C_{20}H_{33}NO_2$: N, 4.40. Found: N, 4.47.

Mixed n-butylisobutoxyhexenylamines. A mixture of 450 g. of *n*-butylamine and 210 g. of mixed isobutoxychlorohexenes was boiled under reflux for twenty-three hours. Upon cooling, the product was treated with a solution of 60 g. of sodium hydroxide in 300 cc. of water, dried over potassium hydroxide and distilled to give 163 g. (65%) of crude *n*-butylisobutoxyhexenylamines, b.p. 119–145°/13 mm. This product was redistilled to give 45 g.

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[a] These were determined by the bromide–bromate method. See Mulliken and Wakeman, *Ind. Eng. Chem., Anal. Ed.*, 7, 59 (1935).

TABLE III

ESTERS

COMPOUND	B.P., °C/MM.	n_D^{25}	d_{25}^{25}	% YIELD	CALC'D*		FOUND	
					C	H	C	H
5-*n*-Butoxy-2-penten-1-yl acetate	96–97/2.3	1.4392	0.937	88	66.0	10.0	66.2	10.1
5-Isobutoxy-2-hexen-1-yl acetate	92–94/2	1.4327		58	67.3	10.3	67.1	10.1
5-Isobutoxy-1-hexyl acetate	100–102/4	1.4210	0.901	75	66.7	11.1	66.5	10.8
5-*n*-Butoxy-2-penten-1-yl adipate	—	1.4604	0.983	61	67.6	9.85	66.4	10.2
5-*n*-Butoxy-1-pentyl adipate	182–190/0.10	1.4466	0.969	32	66.9	10.7	66.9	11.1
5-*n*-Butoxy-1-pentyl terephthalate	230–238/0.35	1.4836	1.008	72	69.3	9.3	69.4	9.3
5-*n*-Pentyloxy-1-pentyl adipate	202–204/0.15	1.4474	0.952	92	68.2	10.9	68.1	11.1
5-Ethoxy-1-hexyl phthalate	197–201/0.2	1.4829	1.032	73	68.3	9.0	67.8	8.8
5-*n*-Butoxy-1-hexyl adipate	214–218/0.5	1.4460	0.950	81	68.1	10.9	68.1	11.7
5-Isobutoxy-1-hexyl adipate	205–215/0.8	1.4433	0.947	81	68.1	10.9	67.4	10.6
5-Isobutoxy-1-hexyl 4-ketopimelate	229–235/0.3	1.4480	0.974	49	66.7	10.3	67.2	9.7

of forerun, b.p. 110–132°/13 mm., and then 113 g. of *n*-butylisobutoxyhexylamine, b.p. 132–140°/13 mm., n_D^{25} 1.4410.

Anal. Calc'd for $C_{14}H_{29}NO$: C, 74.1; H, 12.8.
Found: C, 73.5; H, 12.2.

Mixed n-butylisobutoxyhexylamines. The above 113 g. of *n*-butylisobutoxyhexenylamines was charged to a rocking-autoclave with 10 g. of Raney nickel and 120 cc. of ethanol and shaken with hydrogen for two hours at 70° under 1000 lbs. pressure. The mixture was filtered and distilled to give 98 g. (86%) of *n*-butylisobutoxyhexylamines, b.p. 98–100°/0.3 mm., n_D^{25} 1.4317.

Anal. Calc'd for $C_{14}H_{31}NO$: C, 73.3; H, 13.5.
Found: C, 72.9; H, 12.9.

The *benzenesulfonamide* was prepared by treating the above 98 g. with a solution of 30 g. of sodium hydroxide in 300 cc. of water and with 100 g. of benzenesulfonyl chloride, according to the Schotten-Bauman method. The product was 144 g. (95%) of an undistillable yellow oil, n_D^{25} 1.4905, which was purified by treatment successively with aqueous hydrochloric acid, aqueous sodium hydroxide, decolorizing carbon, and activated alumina.

Anal. Calc'd for $C_{20}H_{35}NO_3S$: S, 8.7. Found: S, 8.8.

5-Methoxy-1-pentenyl-3-isothiocyanate was prepared by refluxing for two hours a mixture of 100 g. of ammonium thiocyanate, 300 cc. of ethanol, and 134 g. of 5-methoxy-1-chloro-2-pentene. After the alcohol was distilled, the residue was cooled, diluted with 100 cc. of ether and filtered. Distillation of the ethereal filtrate gave 107 g. (68%) of 5-methoxy-1-pentenyl-3-isothiocyanate, b.p. 85–90°/5 mm. An analytical sample boiled at 87–88°/5 mm., n_D^{25} 1.5020, d_{25}^{25} 1.016.

Anal. Calc'd for $C_7H_{11}NOS$: S, 21.0. Found: S, 21.1.

5-Methoxy-2-pentenyl-1-isothiocyanate. A mixture of 100 g. of ammonium thiocyanate, 300 cc. of ethanol, and 134 g. of 5-methoxy-2-chloro-1-pentene was boiled under reflux for two hours. After the alcohol was distilled, the residue was cooled, diluted with 100 cc. of ether and filtered. Distillation of the ether solution yielded 91 g. (58%) of crude methoxypentenylisothiocyanates, b.p. 93–110°/16 mm. From this mixture there was obtained by careful refractionation 15 g. of 5-methoxy-1-pentenyl-3-isothiocyanate, b.p. 86–89°/5 mm., n_D^{25} 1.5021 and 25 g. of 5-methoxy-2-pentenyl-1-isothiocyanate, b.p. 105–107°/5 mm., n_D^{25} 1.5154, d_{25}^{25} 1.031.

Anal. Calc'd for $C_7H_{11}NOS$: S, 21.0. Found: S, 20.7.

5-n-Butoxy-1-pentenyl-3-isothiocyanate was prepared by the same procedure using 88.5 g. of 5-*n*-butoxy-1-chloro-2-pentene, 51 g. of ammonium thiocyanate, and 200 cc. of ethanol. The crude yield was 85 g. (86%), b.p. 90–114°/2 mm. An analytical sample boiled at 118–119°/5 mm., n_D^{25} 1.4880, d_{25}^{25} 0.960.

Anal. Calc'd for $C_{10}H_{17}NOS$: S, 16.5. Found: S, 17.0.

5-n-Butoxy-2-pentenyl-1-isothiocyanate was prepared by the same method from 88.5 g. of 5-*n*-butoxy-3-chloro-1-pentene. The yield was 69 g. (69%), b.p. 94–126°/2–2.5 mm. An analytical sample boiled at 136–140°/5 mm., n_D^{25} 1.4985, d_{25}^{25} 0.976.

Anal. Calc'd for $C_{10}H_{17}NOS$: S, 16.5. Found: S, 16.4.

All four of these isothiocyanates gave a strong positive test for the isothiocyanate group (8) and a negative test for the thiocyanate group (9).

SUMMARY

Twelve α-chloroethers have been added to butadiene in the presence of zinc chloride to give 61–86% yields of mixtures of the corresponding 5-alkoxy-3-chloro-1-alkenes and the 5-alkoxy-1-chloro-2-alkenes. The preparation of esters, alcohols, amines, and isothiocyanates from these compounds is described.

DAYTON 7, OHIO

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

THE REARRANGEMENT OF 2-CHLOROISOPROPYL PHENYL SULFIDE

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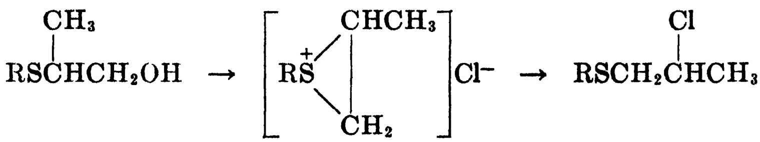
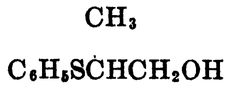
It has been shown that treatment of 2-hydroxyethyl 2-hydroxyisopropyl sulfide and ethyl 2-hydroxyisopropyl sulfide with hydrochloric acid or thionyl chloride yields 2-chloroethyl 2-chloro-*n*-propyl sulfide and ethyl 2-chloro-*n*-propyl sulfide, respectively, instead of the expected isopropyl sulfides (I).[2] It was postulated that the rearrangement proceeds through a cyclic sulfonium intermediate (I).



I

Conversely, rearrangement of an *n*-propyl structure to an isopropyl structure is involved in the ring contraction of 6-hydroxy-1,4-dithiacycloheptane to 2-chloromethyl-1,4-dithian (2). Similar rearrangements, presumably involving the intermediate formation of ethylenimonium compounds, have been observed with a number of β-chloro amines (3).

Several observations recorded in the literature indicate that the isomerization of the isopropyl structure to the *n*-propyl structure, encountered in open-chain *alkyl* β-chloro sulfides, may not occur if an *aryl* group is attached to the sulfur atom. The 2,3-*bis*-(phenylmercapto)-1-halopropanes, the preparation of which has been reported (4), contain such an aryl grouping and would be expected to rearrange to 1,3-*bis*-(phenylmercapto)-2-halopropanes if the rearrangement is general. Also the intermediate sulfonium salt may not form since it has been found that certain aryl ω-haloalkyl sulfides form cyclic sulfonium salts less readily than do the corresponding alkyl ω-haloalkyl sulfides (5). In order to determine whether the presence of an aryl group does prevent rearrangement, a study was undertaken of 2-hydroxyisopropyl phenyl sulfide (II), the hydroxy sulfide which would give the simplest aryl β-chloro sulfide with the requisite structure for isomerization. We have found that treatment of this hydroxy sulfide with thionyl chloride does give the rearranged product, 2-chloro-*n*-propyl phenyl sulfide (III), instead of 2-chloroisopropyl phenyl sulfide (IV).



II

III

IV

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[2] Woodward and co-workers, *J. Chem. Soc.*, 38, 47 (1948) prepared the chlorosulfide from 2-hydroxyethyl 2-hydroxyisopropyl sulfide but did not observe the rearrangement.

2-Hydroxyisopropyl phenyl sulfide (II) was prepared by condensing thiophenol with allyl alcohol in the presence of sulfur. The addition of mercapto compounds to olefins is known to proceed according to Markovnikov's rule in the presence of sulfur (6). Moreover, our product proved to be different from 3-hydroxy-*n*-propyl phenyl sulfide (7), the other possible addition product.

2-Hydroxy-*n*-propyl phenyl sulfide (VI), an oil, was made by an unequivocal method; acetonyl phenyl sulfide (V), prepared from sodium phenyl mercaptide and chloroacetone, was reduced with aluminum isopropoxide under mild conditions.

$$C_6H_5SNa + ClCH_2\overset{\overset{\displaystyle O}{\|}}{C}CH_3 \rightarrow \underset{\displaystyle V}{C_6H_5SCH_2\overset{\overset{\displaystyle O}{\|}}{C}CH_3} \rightarrow \underset{\displaystyle VI}{C_6H_5SCH_2\overset{\overset{\displaystyle OH}{|}}{C}HCH_3}$$

The conversion of 2-hydroxyisopropyl phenyl sulfide (II) to a chlorosulfide was effected in 83% yield by use of thionyl chloride. That rearrangement occurred, giving 2-chloro-*n*-propyl phenyl sulfide (III) instead of 2-chloroisopropyl phenyl sulfide (IV), was shown by several reactions. The chloro sulfide was oxidized to a chloro sulfone by the usual method in 75% yield. Formation of the sulfone served to prevent any further rearrangement since this grouping no longer can form a sulfonium salt. That the chloro sulfone was 2-chloro-*n*-propyl phenyl sulfone (VII), was shown by hydrolysis with sodium carbonate solution and conversion of the unisolated hydrolysis product to the 3,5-dinitro ester (IXb), m.p. 184.5–185.5°. The ester was obtained in only 15% yield based on the chloro sulfone, but no other product was isolated. It was found to be identical with the 3,5-dinitrobenzoate (IXa) prepared from 2-hydroxy-*n*-propyl phenyl sulfone (VIII). Nitration of the chloro sulfone produced a 77% yield of a solid nitro derivative, presumed to be 2-chloro-*n*-nitrophenyl sulfone (X) since phenyl sulfones are known to yield the *m*-nitro derivatives almost exclusively (9).

Reactions used to characterize the chloro sulfide were also found to yield derivatives of 2-hydroxy-*n*-propyl phenyl sulfide (VI). Condensation of the chloro sulfide with sodium *p*-nitrobenzoate or partial hydrolysis followed by treatment with *p*-nitrobenzoyl chloride gave products which were found to be identical with the *p*-nitrobenzoate of 2-hydroxy-*n*-propyl phenyl sulfide.

EXPERIMENTAL

All melting points are uncorrected.

2-Hydroxyisopropyl phenyl sulfide (II). This compound was prepared by a modification of the method used for the synthesis of 2-hydroxyethyl 2-hydroxyisopropyl sulfide (1). A solution of 55.1 g. (0.5 mole) of thiophenol, 34.8 g. (0.6 mole) of allyl alcohol, and 0.5 g. of sulfur was heated under reflux for twenty-four hours. An ether solution of the crude product was washed with 5% sodium hydroxide solution and with water, and then dried over magnesium sulfate. Removal of the ether and distillation of the residue from a Claisen flask yielded 44.0 g. (52%) of the hydroxy sulfide; b.p. 100–114° (0.5–0.7 mm.). Fractionation of a sample through a 10-cm., vacuum-jacketed, Vigreux column gave an almost colorless oil with a pleasant sulfide odor; b.p. 98–100° (0.5 mm.); n_D^{20} 1.5710; d_{20}^{20} 1.103; MR_D 50.14. Calc'd for $C_9H_{12}OS$: MR_D 49.66.

Anal. Calc'd for $C_9H_{12}OS$: C, 64.24; H, 7.19; S, 19.05.
Found: C, 64.28; H, 7.29; S, 18.92.

The *sulfide p-nitrobenzoate* (XI) was made from 1.7 g. of the hydroxy sulfide (II) by the general procedure for preparing esters using an acid chloride and pyridine (10). Less than one gram of the white crystalline product remained after three recrystallizations from dilute ethyl alcohol; m.p. 47–48°.

Anal. Calc'd for $C_{16}H_{15}NO_4S$: C, 60.55; H, 4.76; N, 4.41; S, 10.10.
Found: C, 60.69; H, 4.73; N, 4.11; S, 10.28.

The *sulfone p-nitrobenzoate* (XIIa) was produced when a mixture of 0.3 g. of the sulfide ester (XI), 1.0 g. of 30% hydrogen peroxide solution, and 3 ml. of acetone was heated under reflux for eight hours. After distillation of the acetone the crude solid was recrystallized twice from dilute ethyl alcohol and once from 95% ethyl alcohol. The white crystalline sulfone melted at 112–113°.

Anal. Calc'd for $C_{16}H_{15}NO_6S$: C, 55.01; H, 4.33; N, 4.01; S, 9.18.
Found: C, 55.06; H, 4.37; N, 3.99; S, 8.98.

The *hydroxy sulfone* (XIII) was prepared by slowly adding, with cooling and stirring, 17.0 g. of 30% hydrogen peroxide solution to 8.4 g. of the hydroxy sulfide (II) dissolved in 100 ml. of glacial acetic acid. After the initial heat of reaction had dissipated, the solution was heated overnight at 60–70°. Distillation of the solvents under diminished pressure gave the theoretical amount of residue, which failed to crystallize and boiled at 164–170° (1.2 mm.). 2-Hydroxyisopropyl phenyl sulfone is reported to melt at 46° (11).[3]

The *sulfone benzoate* (XIV) was obtained from 1.0 g. of the undistilled hydroxy sulfone (XIII) by the method of Otto (11). Less than one gram of white crystals remained after three recrystallizations from dilute ethyl alcohol; m.p. 80.5–81.5°. Otto reports the melting point as 71–72°.

Anal. Calc'd for $C_{16}H_{16}O_4S$: C, 63.14; H, 5.30; S, 10.53.
Found: C, 63.28; H, 5.57; S, 10.35.

The *sulfone p-nitrobenzoate* (XIIb) obtained previously by oxidation of the sulfide *p*-nitrobenzoate (XI) also was synthesized from 1.0 g. of the undistilled hydroxy sulfone (XIII) by the general procedure involving the use of pyridine (10). Four recrystallizations of the crude product from ethyl alcohol gave about two-tenths gram of white crystals; m.p. 112–113°. A mixture of this ester with the sulfone *p*-nitrobenzoate (XIIa), prepared from the sulfide ester, melted at 112–113°.

The *sulfone 3,5-dinitrobenzoate* (XV) was prepared from 2.0 g. of the undistilled hydroxy sulfone (XIII) by use of 3,5-dinitrobenzoyl chloride and pyridine (10). About two grams of white crystals remained after two recrystallizations from ethyl alcohol; m.p. 121.5–122.5°.

Anal. Calc'd for $C_{16}H_{14}N_2O_8S$: C, 48.73; H, 3.59; N, 7.11; S, 8.13.
Found: C, 49.23; H, 3.72; N, 7.28; S, 8.31.

2-Hydroxy-n-propyl phenyl sulfide (VI). Acetonyl phenyl sulfide (V) was prepared in 86% yield from 1.0 molar quantities of sodium phenyl mercaptide and chloroacetone by the procedure of Autenrieth (12); b.p. 83–87° (0.3–0.5 mm.); m.p. 32–35°. Fractionation of a sample through a 10-cm., vacuum-jacketed, Vigreux column gave an almost colorless product; b.p. 87° (0.4 mm.); m.p. 35–36°. *Acetonyl phenyl sulfide* has been reported to melt at 34–35° (13) and 36° (12).

The *keto sulfone* (XVI) was prepared from 1.7 g. of the keto sulfide (V) by oxidation with hydrogen peroxide in glacial acetic acid in the usual manner. Recrystallization from water gave a white crystalline product; m.p. 55.5–56.5°. *Acetonyl phenyl sulfone* is reported to melt at 56–57° (13, 14).

The reduction of acetonyl phenyl sulfide (V) was carried out by the procedure employed with acetonyl ethyl sulfide (1). The keto sulfide, 83.0 g. (0.5 mole), and 300 ml. of a 1 *M*

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[3] It is possible that the compound reported by Otto (11) as 2-hydroxyisopropyl phenyl sulfone may be the 2-hydroxy-*n*-propyl phenyl sulfone, a compound also prepared in this investigation and found to melt at 46–47°.

solution of aluminum isopropoxide (15) were used, and the reaction was allowed to continue for forty-eight hours. Distillation of the crude product from a Claisen flask yielded 38.5 g. (46%) of *2-hydroxy-n-propyl phenyl sulfide*, b.p. 87–97° (0.4 mm.). Fractionation of a sample through a 10-cm., vacuum-jacketed, Vigreux column gave a colorless oil with a pleasant odor, b.p. 85.5–86.5° (0.3–0.4 mm.); n_D^{20} 1.5705; d_{20}^{20} 1.103; MR_D 50.21; Calc'd for $C_9H_{12}OS$: 49.66.

Anal. Calc'd for $C_9H_{12}OS$: C, 64.24; H, 7.19.
Found: C, 64.03; H, 7.05.

A number of derivatives of 2-hydroxy-*n*-propyl phenyl sulfide (VI) were obtained by the procedures used for the preparation of the corresponding derivatives of 2-hydroxyisopropyl phenyl sulfide (II).

The *sulfide p-nitrobenzoate* (XVIIa), approximately one-half gram, was obtained from 1.7 g. of the hydroxy sulfide (VI). The white crystalline solid melted at 64.5–65.5° after three recrystallizations from ethyl alcohol.

Anal. Calc'd for $C_{16}H_{15}NO_4S$: C, 60.55; H, 4.76; N, 4.41; S, 10.10.
Found: C, 60.71; H, 4.95; N, 4.44; S, 10.17.

The *sulfone p-nitrobenzoate* (XVIIIa) obtained by oxidation of 0.5 g. of the sulfide ester (XVIIa), melted at 163.5–164.5° after three recrystallizations from ethyl alcohol.

The crude *hydroxy sulfone* (VIII), prepared from 12.6 g. of the hydroxy sulfide (VI) was dissolved in ether, and the ether solution was washed with 5% sodium bicarbonate solution and with water. Distillation of the ether left 14.0 g. (93%) of residue. Two recrystallizations of a small sample of the product from a large volume of petroleum ether (b.p. 30–60°) gave white crystals; m.p. 46–47°.

Anal. Calc'd for $C_9H_{12}O_3S$: C, 53.98; H, 6.04.
Found: C, 54.26; H, 6.26.

The *sulfone benzoate* (XIX), about one-half gram, was prepared from 2.0 g. of the hydroxy sulfone (VIII). The white crystalline product melted at 55–56° after two recrystallizations from 95% ethyl alcohol followed by two recrystallizations from dilute ethyl alcohol.

Anal. Calc'd for $C_{16}H_{16}O_4S$: C, 63.14; H, 5.30; S, 10.53.
Found: C, 63.25; H, 5.47; S, 10.35.

The *sulfone p-nitrobenzoate* (XVIIIb) was prepared from 2.0 g. of the hydroxy sulfone (VIII). Two recrystallizations from 95% ethyl alcohol gave approximately one gram of white crystals; m.p. 163.5–164.5°. A mixture of this compound with the sulfone ester (XVIIIa) obtained from the sulfide ester melted at 163.5–164.5°.

Anal. Calc'd for $C_{16}H_{15}NO_6S$: C, 55.01; H, 4.33; N, 4.01; S, 9.18.
Found: C, 55.15; H, 4.58; N, 3.88; S, 9.21.

The *sulfone 3,5-dinitrobenzoate* (IXa), about one and one-half grams, was obtained from 1.0 g. of the hydroxy sulfone (VIII). The white crystalline product melted at 184.5–185° after two recrystallizations from 95% ethyl alcohol.

Anal. Calc'd for $C_{16}H_{14}N_2O_8S$: C, 48.73; H, 3.59; N, 7.11; S, 8.13.
Found: C, 48.81; H, 3.39; N, 7.04; S, 8.22.

Nitration of the hydroxy sulfone (VIII) by a modification of the procedure of Ipatieff, Pines, and Friedman (9b) for the nitration of alkyl phenyl sulfones gave a compound believed to be *2-hydroxy-n-propyl m-nitrophenyl sulfone nitrate* (XX). One gram of the hydroxy sulfone, dissolved in 4 ml. of concentrated sulfuric acid, was treated with 3 ml. of concentrated nitric acid, added dropwise with swirling over a 15-minute period. After the reaction mixture had cooled to room temperature it was poured on cracked ice and triturated until a solid was obtained. One recrystallization from 50% ethyl alcohol solution gave 1.2 g. of a white crystalline solid, m.p. 90–91°, which corresponds to an 83% yield of the expected product.

Anal. Calc'd for $C_9H_{10}N_2O_7S$: C, 37.24; H, 3.47; N, 9.65; S, 11.05.
Found: C, 37.38; H, 3.35; N, 9.54; S, 11.08.

2-Chloro-n-propyl phenyl sulfide (III), the chloro sulfide from 2-hydroxyisopropyl phenyl sulfide (II). A modification of the procedure of Fuson, Price, and Burness (1) for the

conversion of hydroxy sulfides to chloro sulfides was employed. The reaction was carried out in the hood because of the possible vesicant properties of the product. A solution of 16.8 g. (0.1 mole) of 2-hydroxyisopropyl phenyl sulfide (II) in 25 ml. of dry chloroform was treated with 9.2 g. (0.11 mole) of colorless thionyl chloride, dissolved in 15 ml. of dry chloroform. After removal of the solvent and excess thionyl chloride the crude product was fractionated through a 10-cm., vacuum-jacketed, Vigreux column; b.p. 83–86° (0.1–0.2 mm.); yield 15.5 g. (83%). The product was a colorless oil with a characteristic odor; n_D^{20} 1.5680.

Anal. Calc'd for $C_9H_{11}ClS$: C, 57.90; H, 5.94; Cl, 18.99; S, 17.17.

Found: C, 57.83; H, 5.90; Cl, 18.94; S, 17.43.

2-Hydroxy-n-propyl phenyl sulfide p-nitrobenzoate (XVIIb) from 2-chloro-n-propyl phenyl sulfide (III). This derivative was prepared by a modification of the general procedure for the formation of esters from alkyl halides and salts of acids (16). A solution of sodium ethoxide was prepared from 0.23 g. of sodium metal and 10 ml. of absolute ethyl alcohol, and 1.84 g. of *p*-nitrobenzoic acid was added. The mixture was swirled for five minutes to complete the formation of the salt, and 1.87 g. of the chloro sulfide (III) was added. The heterogeneous mixture was heated under reflux for one and one-half hours, and the solvent was distilled on a steam-bath. The residue was extracted with ether, the ether extract was washed with 5% sodium bicarbonate solution and with water, and the ether was removed on a steam-bath. Recrystallization of the product three times from 95% ethyl alcohol yielded about one-half gram of white crystals; m.p. 64–65°. A mixture of this product with the 2-hydroxy-*n*-propyl phenyl sulfide *p*-nitrobenzoate (XVIIa) prepared previously melted at 64–65°.

Oxidation of 0.4 g. of this sulfide *p*-nitrobenzoate (XVIIb) to the *sulfone p-nitrobenzoate* (XVIIIc) was carried out as previously indicated (XVIIa → XVIIIa). Two recrystallizations of the crude product from 95% ethyl alcohol left 0.3 g. of white crystals; m.p. 163.5–164.5°. Mixtures of this product with the samples of 2-hydroxy-*n*-propyl phenyl sulfone *p*-nitrobenzoate (XVIIIa and XVIIIb) prepared previously melted at 163.5–164.5°.

Hydrolysis of 2-chloro-n-propyl phenyl sulfide (III) and conversion of the product to 2-hydroxy-n-propyl phenyl sulfide p-nitrobenzoate (XVIIc). The hydrolysis was carried out by a modification of the method used for the hydrolysis of 2-chloroethyl 2,2-dichloroethyl sulfide (17). The undistilled chloro sulfide (III), obtained from 25.2 g. of 2-hydroxyisopropyl sulfide, was stirred for two days with a solution of 12.6 g. of sodium bicarbonate in 2 l. of water. The reaction mixture was extracted with ether, the ether extract was washed with water and dried over magnesium sulfate, and the ether was removed on a steam-bath. Distillation of the crude product produced 18 g. of a colorless oil; b.p. 98–106° (1.0–1.5 mm.). The product must have contained some unchanged chloro sulfide since it gave a positive test for halogen with silver nitrate solution.

2-Hydroxy-n-propyl phenyl sulfide p-nitrobenzoate (XVIIc), about three-tenths gram, was obtained from 5 g. of the hydrolysis product and *p*-nitrobenzoyl chloride. After four recrystallizations from 95% ethyl alcohol it melted at 64.5–65.5°. A mixture of this product with the *p*-nitrobenzoate (XVIIb) prepared from 2-hydroxy-*n*-propyl phenyl sulfide (VI) melted at 64.5–65.5°.

The *sulfone p-nitrobenzoate* (XVIIId) was obtained from 0.3 g. of the above sulfide ester (XVIIc) in the usual manner. It melted at 163.5–164.5° after two recrystallizations from 95% ethyl alcohol. Mixtures of this product with other samples (XVIIIa, XVIIIb, and XVIIIc) of 2-hydroxy-*n*-propyl phenyl sulfone *p*-nitrobenzoate melted at 163.5–164.5°.

2-Chloro-n-propyl phenyl sulfone (VII). Oxidation of 15.5 g. of the chloro sulfide (III) was carried out by treatment with 28.3 g. of 30% hydrogen peroxide solution in 60 ml. of glacial acetic acid. After removal of the solvents the crude product was distilled through a 10-cm., vacuum-jacketed, Vigreux column. The colorless oil boiled between 130° and 138° at 0.2–0.4 mm. The yield was 13.5 g. (75%).

Anal. Calc'd for $C_9H_{11}ClO_2S$, C, 49.42; H, 5.07; Cl, 16.21; S, 14.66.

Found: C, 49.41; H, 4.96; Cl, 16.16; S, 14.76.

Nitration of the chlorosulfone (VII) by the procedure employed for the preparation of

2-hydroxy-*n*-propyl *m*-nitrophenyl sulfone nitrate (XX) produced a compound thought to be *2-chloro-n-propyl m-nitrophenyl sulfone* (X). From 0.8 g. of the chloro sulfone 0.75 g. (77%) of white crystals was obtained after two recrystallizations from 50% ethyl alcohol solution, m.p. 72.5–73.5°.

Anal. Calc'd for $C_9H_{10}ClNO_4S$: C, 40.99; H, 3.82; N, 5.31; Cl, 13.45; S, 12.16.
Found: C, 41.15; H, 3.81; N, 5.44; Cl, 13.48; S, 12.41.

Hydrolysis of 2-chloro-n-propyl phenyl sulfone (VII) and conversion of the product to 2-hydroxy-n-propyl phenyl sulfone 3,5-dinitrobenzoate (IXb). A mixture of 2.2 g. of the chloro sulfone (VII), 200 ml. of 0.1 *N* sodium carbonate solution, and 0.2 g. of potassium iodide was heated under reflux for two and one-half hours. The resulting homogeneous solution was extracted with ether. The ether solution was washed with water and dried over sodium sulfate. The residue obtained by removal of the ether was treated with 3,5-dinitrobenzoyl chloride in the usual manner. After four recrystallizations from ethyl alcohol 0.6 g. (15%) of the white crystalline ester was obtained; m.p. 184.5–185°. A mixture of this product with the 2-hydroxy-*n*-propyl phenyl sulfone 3,5-dinitrobenzoate (IXa) prepared previously melted at 184.5–185°.

SUMMARY

2-Hydroxyisopropyl phenyl sulfide undergoes rearrangement to give 2-chloro-*n*-propyl phenyl sulfide when treated with thionyl chloride.

The structure of the product was shown by oxidation of the chloro sulfide to the chloro sulfone, hydrolysis of the chloro sulfone to the hydroxy sulfone, and treatment of the hydroxy sulfone with 3,5-dinitrobenzoyl chloride. The 3,5-dinitrobenzoate was found to be identical with that of 2-hydroxy-*n*-propyl phenyl sulfone.

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[Contribution from the Department of Chemistry of Western Kentucky State College]

THE POLAROGRAPHIC BEHAVIOR OF ISATIN

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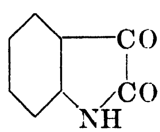
Although polarographic studies of many organic compounds have been reported (1) including studies of keto-enol tautomerism (2) no such studies have been made of lactim–lactam types. It was felt that studies of the behavior of compounds of this type in the polarographic cell might serve to establish the existence of such tautomers in solutions of the compounds.

Isatin seemed ideally suited to this purpose since it contains the essential —CO—NH— grouping and since the *beta*-carbonyl group is readily reducible. To this end polarographic studies were conducted on carefully buffered solutions of isatin.



EXPERIMENTAL

All polarographic data were taken with a Fisher Electropode which was operated manually. A piece of marine barometer tubing about 12 cm. in length was used as a capillary. A stock solution of 0.002 *M* isatin was used in the polarographic work and this solution was diluted to 0.001 *M* by mixing with an equal volume of the desired buffer solution. McIlvaine's standard buffer solutions were used in the *p*H range 2.2 to 8.0 and mixtures of sodium borate and sodium hydroxide solutions were used as buffers in the range 8.0 to 12.0.

The *p*H values of all solutions were determined with a Beckman *p*H meter using a glass electrode. The values reported for alcoholic solutions are "apparent values" not corrected for the nonaqueous solvent errors.

Removal of oxygen from the cell solutions was accomplished by passing natural gas through the solutions for a period of ten minutes before taking the polarographic data. The polarographic cell was maintained in an atmosphere of natural gas during the measurements to prevent absorption of oxygen. The natural gas was passed through an absorption train consisting of a solution of lead acetate, an alkaline solution of pyrogallol, a soda-lime tube and finally through a sample of the cell solution before entering the polarographic cell. All measurements were made with the polarographic cell connected to the saturated calomel electrode by means of an agar bridge saturated with potassium chloride. All measurements were made at a constant temperature of 25 ± 0.25°. The resistance of the polarographic cell and bridge was of the order of 2000 ohms. The applied voltage was accurate to ± 0.005 volts.

Results. The results obtained with a solution of isatin 0.001 *M* and buffered at *p*H 7.10 are shown in Fig. 1. Curve 1, obtained with a freshly mixed solution,

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exhibits four distinct waves. A second polarogram (curve 2) run on this solution after standing twenty-four hours exhibits only the two waves obtained at higher negative potentials. The solution which was originally yellow in color has now become nearly colorless. In the sequel the four waves shown in Fig. 1 are referred to as waves A, A′, C, and D respectively, wave A being the wave observed at lowest potential and wave D that observed at highest potential. The initial and equilibrium polarograms given by a solution of isatin buffered at *p*H 8.00 are shown in Fig. 2. These polarograms exhibit waves due to the same molecular (or ionic) varieties as did the solutions buffered at *p*H 7.10.

The time required for equilibrium to be established varies with the *p*H value at which the solution is buffered and also with the buffer employed. In general

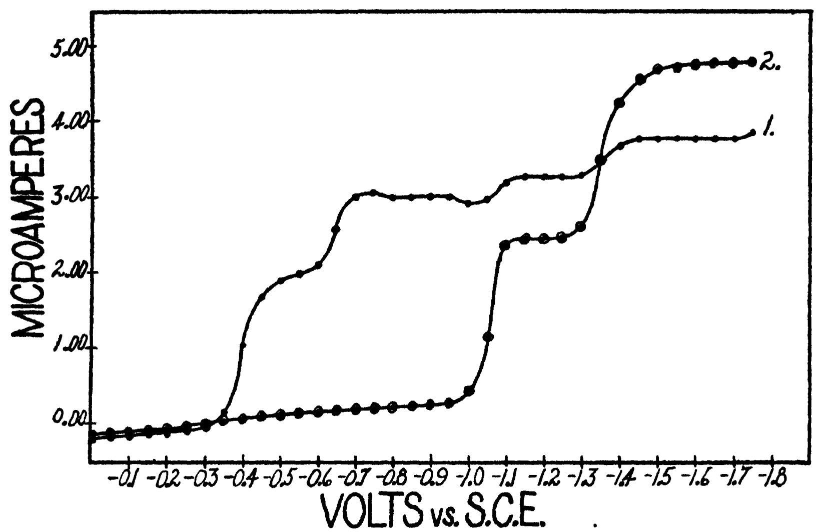


FIG. 1. 0.001 *M* SOLUTION OF ISATIN BUFFERED AT *p*H 7.10
Curve 1, initial polarogram. Curve 2, equilibrium polarogram.

equilibrium is established more rapidly as *p*H is increased and more rapidly when phosphate buffers are employed than when borate buffers are used. Seemingly the opening of the lactam ring is catalysed by phosphate ion. In all cases equilibrium can be established more quickly by heating the solution on the steam-bath for several hours.

A solution buffered at *p*H 4.00 gave a polarogram (Curve 1, Fig. 3) exhibiting three waves (A, A′, and B). The polarographic behavior of this solution did not change on standing.

The polarographic behavior of a solution of isatin buffered at *p*H 2.88 is shown in Fig. 4. Curve 1 shows the behavior (waves A, A′, and B) of a freshly mixed solution and curve 2 that of a solution after equilibrium has been established (waves A and A′ only).

In Fig. 3 the equilibrium curves of solutions buffered at *p*H values of 4.00,

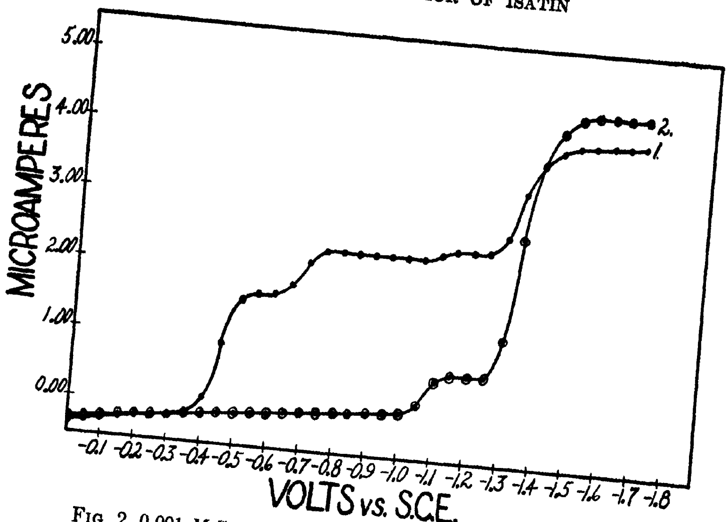


FIG 2. 0.001 M SOLUTION OF ISATIN BUFFERED AT pH 8.00
Curve 1, initial polarogram. Curve 2, polarogram at equilibrium.

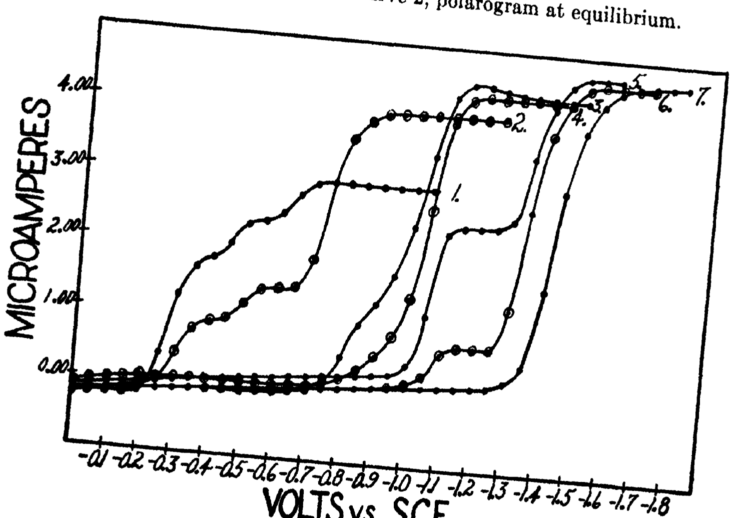


FIG. 3. 0.001 M SOLUTION OF ISATIN. EQUILIBRIUM POLAROGRAMS
Curve 1, buffered at pH 4.00. Curve 2, buffered at pH 4.35. Curve 3, buffered at pH 5.43. Curve 4, buffered at pH 5.83. Curve 5, buffered at pH 7.10. Curve 6, buffered at pH 8.00. Curve 7, buffered at pH 9.75.

4.35, 5.43, 5.83, 7.10, 8.00, and 9.75 are plotted. Curves 1 and 2 exhibit waves A, A′, and B. Curve 3 exhibits waves B and C, while curve 4 shows only wave C. Curves 5 and 6 exhibit waves C and D while curve 7 exhibits only wave D (The explanation for the varying wave heights will be considered in the sequel).

A solution buffered at *p*H 11.60 gives a curve quite like that given by the solution buffered at *p*H 9.75 except that the single wave (D) appears at a potential slightly more negative.

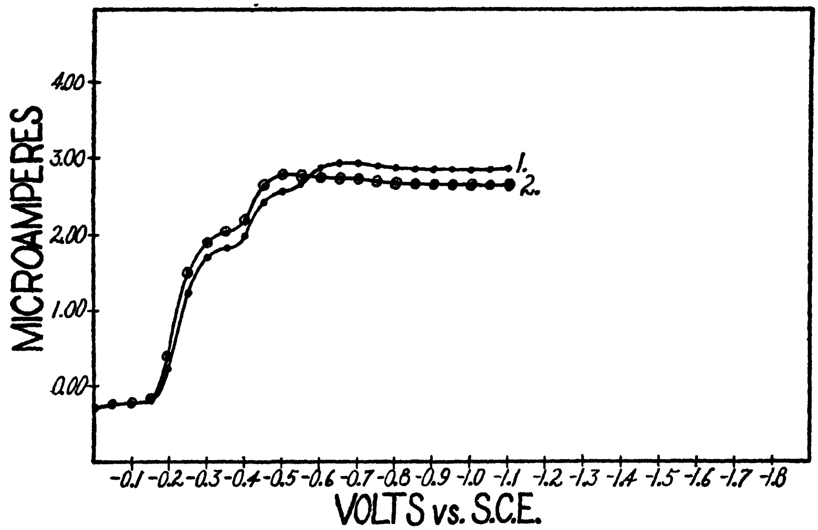


FIG. 4. 0.001 *M* SOLUTION OF ISATIN BUFFERED AT *p*H 2.88
Curve 1, initial polarogram. Curve 2, polarogram at equilibrium.

TABLE I
$E_{\frac{1}{2}}$ VALUES (VOLTS VS. S.C.E.) FOR MOLECULAR VARIETIES A, A′, B, C, AND D

*p*H	MOLECULAR VARIETY				
	A	A′	B	C	D
2.88	−0.22	−0.42			
3.01	−0.23	−0.43	−0.54		
3.40[a]	−0.32				
4.00	−0.28	−0.46	−0.63		
4.35	−0.30	−0.49	−0.74		
5.43			−0.80	−1.02	
5.83				−1.04	
7.10	−0.39	−0.65		−1.06	−1.35
8.00	−0.44	−0.68		−1.08	−1.36
9.75					−1.44
11.10[a]					−1.47

[a] "Apparent" *p*H values uncorrected for nonaqueous solvent errors.

Solutions exhibiting predominantly waves A and A′ are yellow in color. This yellow color disappears as waves A and A′ give way to waves B, C, and D. This disappearance of yellow color has long been supposed to be associated with opening of the lactam ring (3).

The solution of isatin of pH 11.60 becomes a deep reddish-purple color when the solution is first made alkaline but rapidly loses color and is practically colorless by the time the solution has been degassed and is ready to be run polarographically. This solution then exhibits only wave D. The purple color is so transient that polarographic curves could not be obtained on the purple solutions. When the isatin solution is one in 50% ethanol the purple color is much more permanent. The polarographic behavior of these alcoholic solutions is somewhat complex and is now being studied further. The results of these studies will be reported subsequently. The purple color and the polarographic behavior of these solutions provide sufficient evidence to justify the assumption that another molecular variety (variety E) is present in these solutions.

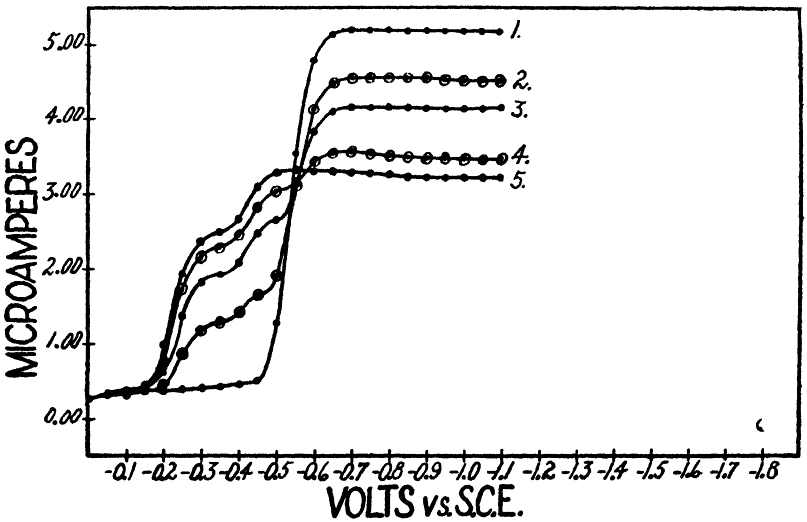


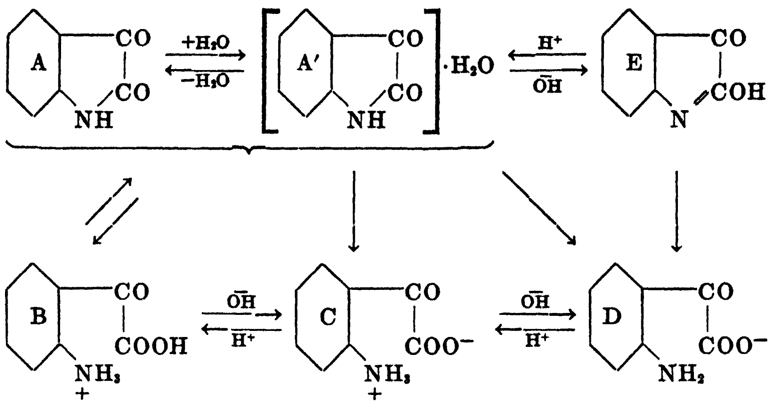
FIG. 5. 0.001 M SOLUTION OF ISATIN BUFFERED AT pH 3.01

Prepared as described in the text. Curve 1 is the initial curve, curve 5 the equilibrium curve, curves 2, 3, and 4 are intermediate curves.

Polarograms exhibiting only wave B can be obtained by preparing the polarographic solution in the following manner. To the isatin stock solution (0.002 M) is added first the alkaline constituent of the McIlvaine standard buffer. The solution is allowed to stand until the yellow color disappears. The citric acid portion of the standard buffer is then added to provide a solution 0.001 M with respect to isatin and buffered at pH 3.01. After degassing, curve 1 of Fig. 5 was obtained in the polarographic cell. As the solution aged curves 2, 3, 4, and 5 were obtained in succession, curve 5 being the equilibrium curve. It will be noticed that wave B alone is exhibited by curve 1 and that this wave gradually gives way to waves A and A′. The equilibrium curve is quite similar to that shown in Fig. 4 for a solution buffered at pH 2.88. In Fig. 4 it will be observed that wave B also disappears as the solution approaches equilibrium.

Discussion. A possible rationalization of this behavior is shown in Chart I. In this rationalization it is postulated that the molecular (or ionic) varieties responsible for the several polarographic waves are: A, the lactam form of isatin; A′, a hydrate of A; B, the cation; C, the dipolar ion; D, the anion; and E, the lactim (or the lactim ion) form of isatin each related to the other as sug-

CHART I



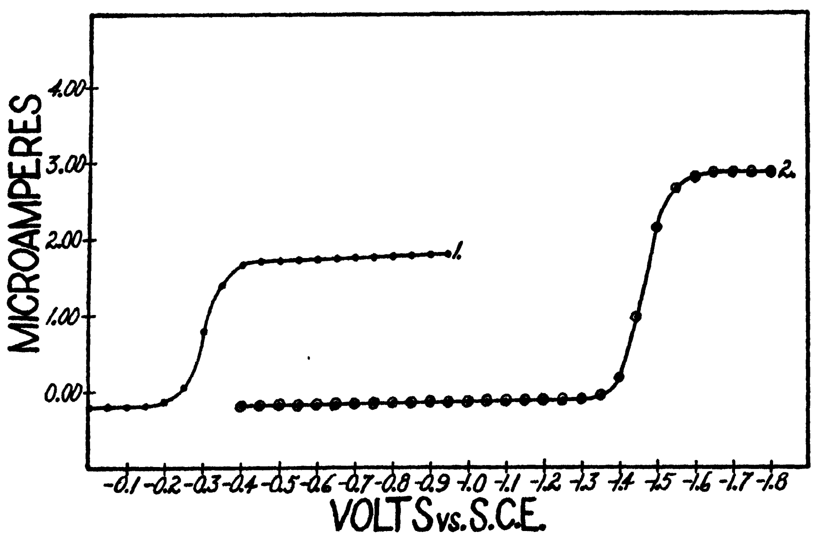


FIG. 6. 0.001 *M* Solution of isatin in 50% ethanol. Both curves are equilibrium curves. Curve 1, buffered at *p*H 3.40. Curve 2, buffered at *p*H 11.10.

gested in Chart I. In support of the postulate that variety A′ is a hydrate of A it was found that wave A′ became successively smaller when solutions containing 10%, 20%, 30%, 40%, and 50% ethanol were employed. In 40% and 50% ethanol solutions no A′ wave was observed. In Fig. 6 curve 1, is shown the polarogram of a solution of isatin (0.001 *M*) in 50% ethanol at an apparent *p*H of 3.40.

Calculation of the number of electrons involved in the reduction by means of the Ilkovic equation. The number of electrons involved in the reduction of a substance at the dropping mercury electrode can be calculated by means of the Ilkovic equation.

$$n = I_d/605\ D^{1/2}\ C\ m^{2/3}\ t^{1/6}$$

Since experimental values for the diffusion coefficient D were not available a value for D was calculated by assuming that Stoke's law holds under the experimental conditions [ref. (1a), p. 48]. The value (1.51) used for the density of isatin was that given by Cox, Goodwin, and Wagstaff (4).

$$\begin{aligned} V_m &= \text{Mol. Wt./density} = 147/1.51 = 97.3 \\ D &= 3.32 \times 10^{-5}/V_m^{1/3} = 3.32 \times 10^{-5}/(97.3)^{1/3} \\ D &= 7.22 \times 10^{-6}\ \text{cm.}^2\ \text{sec.}^{-1} \end{aligned}$$

Calculation of n for the D wave in aqueous solution (Curve 7, Fig. 3)

$$m = 0.9824\ \text{mg./sec.} \qquad t = 5.76\ \text{sec. (at } -1.44\ \text{v.)}$$
$$m^{2/3}\ t^{1/6} = 1.32\ \text{mg.}^{2/3}\ \text{sec.}^{-1/2} \qquad I_d = 4.40\ \text{microamp.}$$
$$n = 4.40/605\ (7.22 \times 10^{-6})^{1/2}\ (1)\ (1.32) = 2.05$$

Calculation of n for the B wave (Curve 1, Fig. 5)

$$m = 0.9824\ \text{mg./sec.} \qquad t = 7.28\ \text{sec. (at } -0.54\ \text{v).}$$
$$m^{2/3}\ t^{1/6} = 1.38\ \text{mg.}^{2/3}\ \text{sec.}^{-1/2} \qquad I_d = 4.60\ \text{microamps.}$$
$$n = 4.60/605\ (7.22 \times 10^{-6})^{1/2}\ (1)\ (1.38) = 2.10$$

Calculation of n for the C wave (Curve 4, Fig. 3)

$$m = 0.9824\ \text{mg./sec.} \qquad t = 6.92\ \text{sec. (at } -1.04\ \text{v.)}$$
$$m^{2/3}\ t^{1/6} = 1.36\ \text{mg.}^{2/3}\ \text{sec.}^{-1/2} \qquad I_d = 4.22\ \text{microamps.}$$
$$n = 4.22/605\ (7.22 \times 10^{-6})^{1/2}\ (1)\ (1.36) = 1.90$$

No calculation of n for the A wave can be made from diffusion currents measured in aqueous solution because in such solutions wave A is always accompanied by wave A′. When solutions in 50% ethanol are employed no evidence of the presence of variety A′ is found and diffusion currents for variety A can be measured.

In such solutions no values are available for the diffusion coefficient D, the values calculated through the use of the Stokes-Einstein equation being valid only for aqueous solutions at 25°. However assuming that wave D in 50% ethanol (curve 2, Fig. 6) represents a two-electron reduction we can calculate a *diffusion coefficient* for isatin in 50% ethanol.

$$m = 0.9824\ \text{mg./sec.} \qquad t = 5.56\ \text{sec. (at } -1.47\ \text{v).}$$
$$m^{2/3}\ t^{1/6} = 1.32\ \text{mg.}^{2/3}\ \text{sec.}^{-1/2} \qquad I_d = 2.95\ \text{microamps.}$$
$$\begin{aligned} I_d &= 605nCD^{1/2}\ m^{2/3}\ t^{1/6} \\ 2.95 &= 605\ (2)\ (1)\ D^{1/2}\ (1.32) \\ D &= 3.43 \times 10^{-6}\ \text{cm.}^2\ \text{sec.}^{-1} \end{aligned}$$

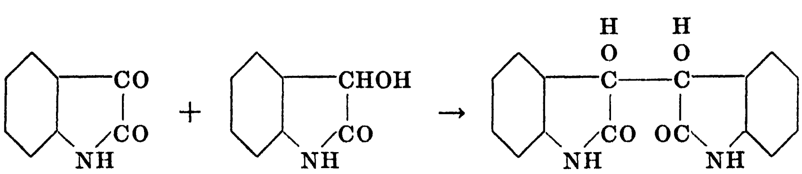
Then from the diffusion current for wave A (curve 1, Fig. 6) we can calculate a value for n.

$$m = 0.9824 \text{ mg./sec.}^{-1} \qquad t = 6.84 \text{ sec. (at } -0.32 \text{ v).}$$
$$m^{2/3}\, t^{1/6} = 1.36 \text{ mg.}^{2/3} \text{ sec.}^{-1/2} \qquad I_d = 1.80 \text{ microamps.}$$
$$n = 1.80/605\ (3.43 \times 10^{-6})^{1/2}\ (1)\ (1.36) = 1.18$$

It is thus rather definitely established that molecular variety A undergoes a one-electron reduction while varieties B, C, and D undergo two-electron reductions. This accounts satisfactorily for the increase in wave height as freshly prepared solutions exhibiting wave A age with wave A giving way to waves B, C, and D.

No calculation of a value of n is possible for variety A′ since this wave cannot be isolated and since the relative concentrations of A and A′ in these solutions are unknown. However, consideration of the relative wave heights in a large number of polarograms exhibiting waves A and A′ leads one to the conclusion that the reduction of A′ (wave A′) is probably a two-electron reduction altho it must be recognized that a rigorous determination of this point has not been possible.

It is by no means surprising that variety A should exhibit a reduction wave corresponding to a one-electron reduction in view of the well known fact that the product of the two-electron reduction of isatin, dioxindole, condenses readily with isatin to give isatin pinacol (isatide).



Thus if variety A undergoes a two-electron reduction to dioxindole which in turn condenses with a molecule of isatin to form isatide the reduction wave exhibited by A will correspond to a one-electron reduction.

It is likewise not at all surprising to find that varieties A′, B, C, and D undergo two-electron reductions and being incapable of condensing with their reduction products exhibit waves corresponding to two-electron reductions.

As previously stated the polarographic behavior of solutions containing variety E (the purple variety) is complex. These solutions are being studied further and it is hoped that quantitative treatment of the polarograms obtained can be given in a later paper. It can only be said now that from the appearance (color) and polarographic behavior of such solutions it is evident that another molecular variety (E) is present. This is thought to be the lactim (or the lactim ion) form of isatin since the N-alkylisatins (in which lactim formation is not possible) do not yield the transient purple color while isatin derivatives like 5-methylisatin, 5-bromoisatin, etc., which contain the —CO—NH— grouping do give this color behavior.

Absorption spectra. Absorption spectra measurements were made on solu-

tions known (from their polarographic behavior) to contain only one molecular (or ionic) variety. The results of these measurements are shown in Fig. 7. The similarity between the curves for varieties B, C, and D is in agreement with the rationalization postulated. Absorption spectra measurements made on isatin

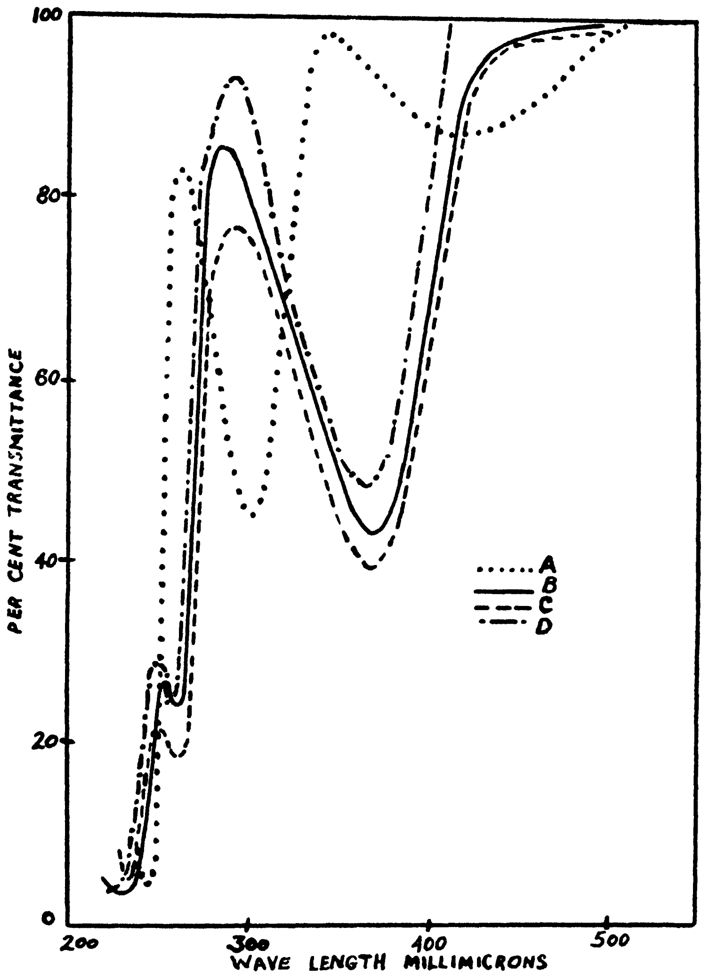


FIG. 7. Curve A. 0.0001 M isatin in 50% ethanol-H_2O buffered at pH 3 00. Curve B. 0.0001 M isatin solution. Variety B isolated temporarily as in polarographic curve 1 of Fig. 5. Curve C. 0.0001 M equilibrated solution of isatin buffered at pH 5.83. Curve D. 0.0001 M equilibrated solution of isatin buffered at pH 11.60.

solutions have been reported previously by several workers (3, 5) but since the data reported by these workers are conflicting and their measurements were made for the most part on solutions which our work shows would certainly contain more than one molecular (or ionic) variety it appears that little value can be attached to the previous measurements. The absorption spectra measure-

ments shown in Fig. 7 were made with a Beckman DU spectrophotometer on solutions 0.0001 *M* with respect to isatin. Cells of 1.0 cm. depth were used.

Acknowledgment. The senior author (W. C. S.) is grateful to the Research Corporation for a grant which has made available the services of his co-workers and which made possible the purchase of necessary equipment.

SUMMARY

Polarographic evidence indicates that solutions of isatin contain (under different conditions) six different molecular or ionic varieties. A rationalization of this behavior has been presented which is in accord with the previously known facts of isatin chemistry.

BOWLING GREEN, KENTUCKY

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[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF SCHERING CORPORATION]

REDUCTIONS WITH NICKEL-ALUMINUM ALLOY AND AQUEOUS ALKALI. PART VII. HYDROGENOLYSIS OF SULFUR COMPOUNDS[1]

DOMENICK PAPA, ERWIN SCHWENK, AND HELEN F. GINSBERG

Received January 4, 1949

Since the remarkable discovery of Bougault, Cattelain, and Chabrier (1) that Raney nickel catalyst brings about hydrogenolysis of sulfur compounds, the reaction has been extensively applied to the elucidation of the structure of several natural products such as biotin (2), penicillin (3), and streptomycin (4). In addition, this hydrogenolysis reaction has found considerable application in synthetic organic chemistry (5).

In a previous publication (6) from this laboratory, it has been reported that sulfonic acid groups and a methylthiol group are readily displaced by hydrogen by the action of nickel-aluminum alloy and aqueous alkali. Under similar conditions, ether linkages as part of heterocyclic ring systems such as the methylenedioxy bridge (7) and furan derivatives (8) are ruptured to phenolic and aliphatic hydroxy compounds respectively. This paper describes the results of studies on this fission reaction with thiophene derivatives as well as other organic sulfur compounds.

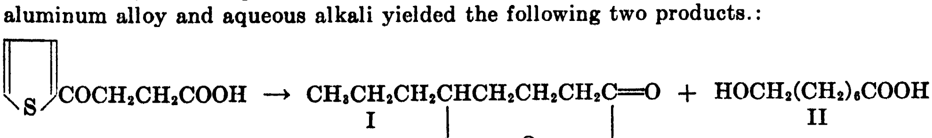
The observation that Raney alloy brings about a rupture of the carbon–sulfur linkage prompted us to investigate the behavior of thiophene derivatives[2] as well as organic sulfides under the conditions of the alloy procedure. β-(α-Thenoyl)-propionic acid[3] (I) on treatment with nickel-aluminum alloy in aqueous alkali solution yielded either a mixture of about equal amounts of γ-ketocaprylic acid (II) and γ-caprylolactone (III) or only the lactone III, the course of the reaction being dependent on the ratio of alloy and I and on the reaction time.

The initial use of insufficient alloy and/or a short reaction time affords only partial conversion of the keto acid (II) to the lactone (III). This result and the

[1] This is part of a paper presented in abstract before the Division of Organic Chemistry at the New York Meeting of the American Chemical Society, September, 1944.

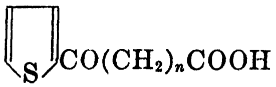
[2] Recently a report of the use of Raney nickel catalyst for the hydrogenolysis of thiophene compounds was published [Blicke and Sheets, *J. Am. Chem. Soc.*, **70**, 3768 (1948)].

[3] In the preliminary announcement of this investigation (Footnote 1) [*Org. Syntheses*, **27**, 70 (1948)] it was reported that β-(α-thenoyl)propionic acid on treatment with nickel-aluminum alloy and aqueous alkali yielded the following two products.:



The analytical data, carbon and hydrogen analyses, and neutral equivalent; the failure to obtain any positive reaction with ketonic reagents, and the known susceptibility of keto groups to the alloy reduction method seemed sufficient preliminary evidence for the formation of products I and II. However, subsequent studies with homologous compounds clearly showed this interpretation of the reaction to be incorrect.

known poisoning effect of sulfur on Raney catalyst are further evidence that the alloy reduction method is essentially a catalytic reaction (*cf.* ref. 10).



I n = 2
IV n = 8

$\longrightarrow$

$$CH_3CH_2CH_2CH_2\underset{\underset{O}{\|}}{C}(CH_2)_nCOOH$$

II n = 2 VI n = 8

$$CH_3CH_2CH_2CH_2\underbrace{CHCH_2CH_2C}_{O}{=}O$$

III

$$CH_3CH_2CH_2CH_2CHOH(CH_2)_8COOH$$

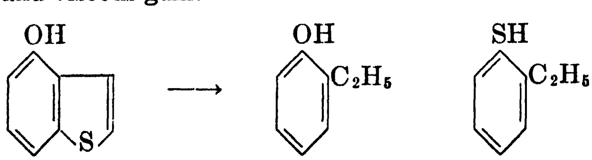
V

However, the higher homologous acid, ω-(α-thenoyl)pelargonic acid (IV) gave only the 10-hydroxymyristic acid (V). With acid I good yields of the lactone (III) could be secured by the use of approximately a 3:1 ratio of alloy to compound I.

The reaction of Raney catalyst on I and IV also gave III and V respectively. However, a 25:1 ratio of catalyst to compound I and IV was used. In the latter reaction none of the keto compounds II and VI were obtained. The structure of VI was confirmed by independent synthesis using the Grignard reaction between *n*-butyl bromide and ω-carbethoxypelargonyl chloride. The hydroxy acid V on oxidation with chromic acid yielded the keto acid VI which was identical with that prepared by the Grignard reaction.

Several thiophenecarboxylic acids and thienylaliphatic acids gave the normal hydrogenolysis products. With several of these compounds the initial hydrogenolysis did not proceed to completion and a second treatment with Raney alloy was necessary in order to obtain products qualitatively free of sulfur. However, in none of these reactions was the amount of Raney alloy used comparable to the excesses of Raney nickel catalyst required for similar hydrogenolyses.

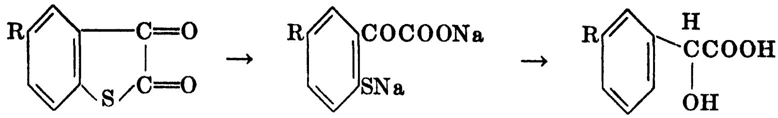
On treatment with Raney alloy, 4-hydroxythianaphthene (VII) gave *o*-ethylphenol (VIII) and viscous gum.



VII VIII IX

Although the latter product gave a positive test for sulfur, no definite crystalline material could be isolated. Thianaphthene has been reduced with sodium and alcohol; and, in addition to the normal reduction product, small amounts of *o*-ethylthiophenol (IX) have been isolated (9). High-pressure hydrogenation of thianaphthene gives a variety of products among which are ethylbenzene and *o*-ethylthiophenol.

The reduction of thianaphthenequinone (X) and the 5-methyl derivative (XII) were studied since these substances possess two carbonyl groups, one of which is adjacent to the ring sulfur atom.



X R = H
XII R = CH_3

XI

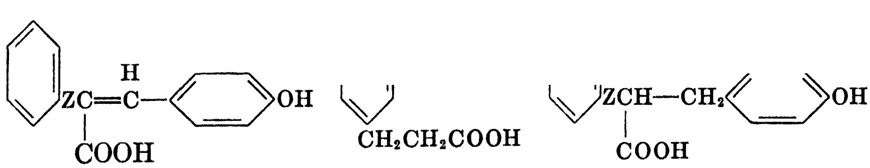
XIII R = H
XIV R = CH_3

However, in alkaline solution, the heterocyclic ring ruptured with the formation of the sodium salt of the glyoxalic acid (XI) prior to any reduction of X and XII. Compound X gave mandelic acid (XIII); and the 5-methyl derivative (XI) gave *m*-methylmandelic acid (XIV).

The failure of the alloy procedure to reduce the α-hydroxy group in the acids XIII and XIV is surprising in view of the ease with which benzyl alcohols (10) may be reduced. Except for the formation of traces of phenylacetic acid, mandelic acid was recovered unchanged after treatment with Raney alloy. It therefore may be assumed that the hydrogenolysis of the sulfhydryl group in XI did not alter the course of the reaction. These results, however, parallel those obtained with the Clemmensen method in that α-keto acids are reduced to the α-hydroxy compounds (11) rather than to the completely reduced compounds.

The hydrogenolysis of organic sulfides and thiophenols with Raney alloy proceeded in good yield, di-*p*-tolyl sulfide and benzyl mercaptan yielding toluene and thiosalicyclic acid and thio-*p*-cresol giving benzoic acid and toluene respectively. With *o*-carboxyphenylthioglycolic acid, it was necessary to repeat the treatment with Raney alloy in order to secure benzoic acid free of any sulfur compound.

The reduction of α-phenylmercapto-*p*-hydroxycinnamic acid (XV) (12) and its oxygen analog (XVI) (12) was investigated since these acids were included in a study of the action of Raney alloy on α,β-diarylacrylic acid. The thio ether XV and ether XVI underwent rupture to yield β-(*p*-hydroxyphenyl)propionic acid (XVII). The dihydro derivative XVIII also gave XVII, whereas XIX was recovered in 60% yield and only a small amount of XVII was obtained.



XV Z = O
XVI Z = S

XVII

XVIII Z = O
XIX Z = S

EXPERIMENTAL

The reductions were carried out as previously described (10). It was necessary to modify the procedure for several compounds and the reduction for these compounds is described in

detail. The yields are calculated to the purified reduction product. Alkali-insoluble compounds were reduced in a 2000-cc. flask equipped with an adapter and efficient reflux condenser. All melting points are corrected.

1. *Reduction of γ-(α-thenoyl)propionic acid.* Twenty grams of this acid (13) in 1000 cc. of 10% sodium hydroxide was reduced with 50 g. of Raney alloy. The acidified solution was extracted with three 250-cc. portions of ether. The combined ether extracts were then extracted with 2% sodium carbonate solution. From the ether solution was obtained 4.6 g. of γ-caprylolactone, b.p. 116–117° (10 mm.), 84–85° (2 mm.), n_D^{25} 1.4420 [literature, b.p. 127° (16 mm.), n_D^{19} 1.4451 (14)].

Anal. Calc'd for $C_8H_{14}O_2$: C, 67.56; H, 9.92.

Found: C, 67.41; H, 10.06.

The *phenylhydrazide* melted at 108–108.5° after recrystallization from chloroform-petroleum ether.

Anal. Calc'd for $C_{14}H_{22}N_2O_2$: N, 11.19. Found: N, 11.25.

The combined sodium carbonate extracts were acidified and extracted with ether. The ether residue amounted to 6.6 g., and distilled at 156–157° (10 mm.). The distillate solidified, and after recrystallization from petroleum ether melted at 54–54.5°; literature m.p. for *γ-ketocaprylic acid,* 53° (15).

Anal. Calc'd for $C_8H_{14}O_3$: C, 60.74; H, 8.87; N.E., 158.

Found: C, 60.47, 60.80; H, 8.91, 9.04; N.E., 158.7.

The *semicarbazone* prepared in the usual manner melted at 155–156° after recrystallization from ethyl alcohol; literature m.p. 153° (16).

The above described reduction was repeated except that the alloy was added over a period of 5–6 hours. The reaction mixture was heated at 70–80° overnight and then filtered. From the acidified filtrate 11.8 g. of γ-caprylolactone, b.p. 83–85° (2 mm.), n_D^{25} 1.4421, was obtained. None of the γ-ketocaprylic acid was obtained in this reaction.

With Raney nickel catalyst (75–80 g.), 5 g. of the β(α-thenoyl)propionic acid in 200 cc. of ethanol at reflux temperature for 5 hours (17) gave 3.5 g. of the γ-caprylolactone, b.p. 80–82° (1 mm.), n_D^{25} 1.4428. The *phenylhydrazide* melted at 107–108°, mixed m.p. with product from Raney alloy reduction 107–108°.

2. *Reduction of ω-(α-thenoyl)pelargonic acid.* Twenty grams (18) of this acid was reduced as described for the corresponding propionic acid compound. The only product isolated was soluble in sodium carbonate solution, crude yield 16 g., m.p. 49.5–52.5°. Recrystallized from a mixture of benzene–petroleum ether the *10-hydroxymyristic acid* melted at 56–57°.

Anal. Calc'd for $C_{14}H_{28}O_3$: C, 68.79; H, 11.56.

Found: C, 68.60, 68.90; H, 11.49, 11.57.

The hydroxy acid (5 g.) was oxidized with 5 g. of chromic acid in 150 cc. of acetic acid at 50–60° essentially as described (19). The keto product was isolated in a crude yield ot 4.6 g., m.p. 67–69°. The *semicarbazone* was prepared in the usual manner, and melted at 159–160° after recrystallization from methanol.

Anal. Calc'd for $C_{15}H_{29}N_3O_3$: N, 14.04. Found: N, 13.91.

Five grams of the pelargonic acid was refluxed for 5 hours with 80 g. of Raney nickel catalyst (17) in 100 cc. ot ethanol. The reaction mixture was worked up as described, and a crude yield of 3.5 g. of the 10-hydroxymyristic acid was obtained. Recrystallized from benzene-petroleum ether, m.p. 54–55°; mixed m.p. with product from the Raney alloy reduction, 54.5–56°.

The *10-ketomyristic acid* was also prepared by the Grignard reaction of ω-carbethoxypelargonyl chloride and *n*-butyl bromide (20). The crude keto acid was separated from sebacic acid by formation of the *semicarbazone.* The latter after recrystallization from methanol melted at 158–159°; mixed m.p. with the product from the chromic acid oxidation 159–160°.

3. *Reduction of γ-(α-thienyl)butyric acid.* To 30 g. of the butyric acid (13a) dissolved in 750 cc. of 10% sodium hydroxide there was added 60 g. of Raney alloy. The reduction was carried out in the usual manner and after acidification of the alkaline solution the reduction

product was extracted with ether. After removing the ether, the residue (26 g.) was fractionated. Fraction I was obtained in a yield of 10 g. and was identified as *caprylic acid;* b.p. 100° (1 mm.), n_D^{24} 1.4352 [literature, b.p. 240°, n_D^{20} 1.4268 (21)]. The *amide* was prepared in the usual manner and melted at 105–105.5° [literature m.p. 106°, 105.5° (21)].

The second fraction amounted to 13 g., b.p. 130–133° (1 mm.), n_D^{21} 1.4982. It was identified by its boiling point, refractive index, and analysis as starting material.

Anal. Calc'd for $C_8H_{10}O_2S$: C, 56.44; H, 5.92.

Found: C, 56.13; H, 5.75.

The *p-bromophenacyl ester* was prepared in the known manner and recrystallized from aqueous alcohol, m.p. 58–59°; mixed m.p. with *p*-bromophenacyl ester of γ-(α-thienyl)-butyric acid, 58–59°.

Anal. Calc'd for $C_{16}H_{15}BrO_3S$: C, 52.32; H, 4.12.

Found: C, 52.13; H, 4.33.

4. *Reduction of β-(α-thienyl)acrylic acid.* This acid was prepared from thiophene aldehyde (22), potassium acetate, and acetic anhydride (23). Twenty grams of the acrylic acid was dissolved in 750 cc. of 10% sodium hydroxide and 50 g. of alloy added. The product isolated from the reaction mixture gave a qualitative test for sulfur and was, therefore, reduced with an additional 25 g. of alloy. The reaction mixture, after filtration and acidification, was extracted with ether. The ether was evaporated and the residue distilled. The first fraction, yield 6 g., b.p. 106–110° (5 mm.), n_D^{20} 1.4215, was identified as *heptylic acid.* The *amide* prepared in the usual manner melted at 95–96° [literature b.p. 223°, n_D^{20} 1.4234; amide m.p. 96°, 96.5° (24)].

5. *Reduction of thiophene-2-carboxylic acid.* Twenty grams of thiophene-2-carboxylic acid was dissolved in 750 cc. of 10% sodium hydroxide and treated with 60 g. of Raney alloy. The reduction product gave a qualitative test for sulfur and the reduction was repeated with the same amounts of alkali and alloy. After filtration of the nickel, the alkaline solution was worked up by the usual method. The oily residue, which amounted to 11 g., was identified as *valeric acid,* b.p. 90–95° (3 mm.), n_D^{20} 1.4088; *p-bromophenacyl ester,* m.p. 64–65° [literature n_D^{20} 1.4086, *p*-bromophenacyl ester, 63° (25)]; mixed m.p. with an authentic sample of valeric acid *p*-bromophenacyl ester, 63–64°.

6. *Reduction of 4-methylthiophene-2-carboxylic acid.* The reduction of 25 g. of this compound was carried out as described for the thiophene-2-carboxylic acid. The reduction product was identified as *4-methylpentanoic acid,* yield 12 g.; b.p. 86–88° (11 mm.), n_D^{24} 1.4133; *p-bromophenacyl ester,* m.p. 78–80° [literature n_D^{20} 1.4144; *p*-bromophenacyl ester 77.3° (26)].

7. *Reduction of 5-methylthiophene-2-carboxylic acid.* Twenty-five grams of this acid was reduced in exactly the same manner as described for the 4-isomer. The reduction product amounted to 13.6 g., and was identified as *caproic acid,* b.p. 90–95° (5 mm.), n_D^{24} 1.4150; *amide* m.p. 98.5–99.5° [For caproic acid, n_D^{20} 1.4163; amide m.p. 100° (27)].

8. *Reduction of 4-hydroxythianaphthene.* Twenty grams of 4-hydroxythianaphthene (13a) was reduced in 750 cc. of 10% sodium hydroxide with 50 g. of nickel-aluminum alloy. After the reduction was completed, the acidified solution was extracted with ether, the ether evaporated, and the residue distilled. Fraction I was obtained in a yield of 7.6 g., b.p. 68–70° (6 mm.). This substance was identified as *o-ethylphenol,* the aryloxy derivative melting at 141–142° [literature m.p. 137–138° (28)]; N.E., 180; Found: 179.8. Fraction II (8.2 g.) boiled over a wide range, partially solidified on cooling and gave a positive test for sulfur. This fraction after treatment with 25 g. of alloy yielded 3.9 g. of *o*-ethylphenol. A considerable residue remained after both distillations and on cooling appeared as a viscous, black gum, giving a positive test for sulfur. This residue was not further investigated.

9. *Reduction of 5-methylthianaphthenequinone.* The preparation of this compound has been previously described (29) and the following, which is a modification of the published procedure, gave substantially better yields. Forty-eight grams of oxalyl chloride in 200 cc. of dry ether was added dropwise to 31 g. of *p*-thiocresol in 250 cc. of dry ether. The mixture

was warmed on the steam-bath, the ether evaporated, and the residue freed from excess oxalyl chloride in a vacuum desiccator over potassium hydroxide. The resulting yellow solid was dissolved in 450 cc. of carbon disulfide, cooled to 0°, and 40 g. of aluminum chloride added. The temperature was allowed to rise to room temperature and after refluxing for one-half hour, the reaction mixture was cooled and decomposed with ice and HCl. The carbon disulfide was steam-distilled off, and the residue recrystallized from methyl alcohol, yield 30 g., m.p. 146–147°. From the methyl alcohol mother liquor an additional 5 g. was obtained, melting at 144–146° [literature m.p. 144° (29)].

Fifteen grams of 5-methylthianaphthenequinone was dissolved in 500 cc. of 10% sodium hydroxide, 40 g. of Raney alloy was added, and the reduction carried out as described. The acidified filtrate was cooled, extracted with ether, and the ether evaporated. The residue (11 g.), which did not couple with nitrodiazobenzene, was recrystallized from a mixture of benzene-petroleum ether, yield 9.8 g.; m.p. 93–94°. This compound was identified as *m-methylmandelic acid*. The literature value for this compound is 84° (30).

Anal. Calc'd for $C_9H_{10}O_3$: C, 65.03; H, 6.07; N.E., 166.

Found: C, 64.95; H, 6.42; N.E., 167.

10. *Preparation and reduction of thianapthenequinone.* Thianaphthenequinone was prepared from thiophenol and oxalyl chloride in accordance with the procedure described for the 5-methyl derivative. The compound, after recrystallization from methyl alcohol, melted at 120–121° (31).

Ten grams of the thianaphthenequinone was reduced in the known manner with 15 g. of alloy and 250 cc. of 10% sodium hydroxide. The alkaline solution after filtration was acidified, thoroughly cooled, and extracted with ether. The residue, on recrystallization from a mixture of benzene and petroleum ether, was obtained in a yield of 5 g., m.p. 117–120°. Recrystallized from chloroform, m.p. 120–121°; mixed melting point with mandelic acid, 120–121°. N.E., 152.6.

11. *Reduction of mandelic acid.* Twenty-five grams of mandelic acid was dissolved in 600 cc. of 10% sodium hydroxide solution, 40 g. of Raney alloy was added, and the reduction completed in the usual manner. After filtration of the nickel, the alkaline solution was acidified, thoroughly cooled, and exhaustively extracted with ether. From the evaporation of the ether, a residue of 21 g. was obtained which melted at 114–116°. Recrystallization from chloroform gave a product melting at 119–120°; mixed melting point with mandelic acid showed no depression; N.E., 153; Found: 152.5. The cooled, acidified solution yielded a small amount of crystalline material which was identified as *phenylacetic acid*, m.p. and and mixed m.p. 75–76°.

12. *Reduction of benzyl mercaptan and di-p-tolyl sulfide.* To a 2-liter flask fitted with an adapter and condenser was added 20 g. of benzyl mercaptan, 500 cc. of 10% sodium hydroxide, and 40 cc. of ethyl alcohol. The mixture was heated to 50° and 40 g. of Raney alloy was added in the course of two to two and one-half hours with frequent and vigorous shaking. The reaction mixture was then heated for two hours and steam-distilled. The distillate was cooled, saturated with salt, and extracted with chloroform. The chloroform extract was dried overnight over calcium chloride; on distillation it yielded 9.2 g. of *toluene*. which was identified by boiling point and oxidation to benzoic acid. The steam-distillation residue was filtered, the residual nickel washed with hot water, and the combined filtrate and washings acidified to Congo Red paper with conc'd HCl. Exhaustive extraction of the acid solution with ether and evaporation of the ether left no residue.

Twenty-five grams of di-*p*-tolyl sulfide when reduced as described above yielded 13 g. of toluene, no alkali-soluble product being detected in the steam-distillation residue.

13. *Reduction of thiosalicylic acid.* To 10 g. of thiosalicylic acid in 300 cc. of 10% sodium hydroxide, there was added 20 g. of Raney alloy. The reduction was carried out as previously described. After filtration, the alkaline solution was acidified to Congo Red paper with HCl and repeatedly extracted with ether. The crude residue from the ether extracts gave 7.6 g. of a product which melted at 96–99° and did not couple with nitrodiazobenzene or give a color reaction with ferric chloride. After recrystallization from water, the product was identified as *benzoic acid*, m.p. and mixed m.p. 122–123°; N.E., 122; Found: 122.

14. *Reduction of p-thiocresol.* Twenty grams of *p*-thiocresol was reduced with 40 g. of alloy and 600 cc. of 10% sodium hydroxide. The reaction was carried out in a 2-liter flask with an adapter carrying a condenser. It was found desirable to add the alloy while the reaction mixture was kept below 40° in order to avoid loss of volatile reaction products. The alloy was placed in an Erlenmeyer flask which was attached to the adapter with Gooch rubber tubing (33). After all the alloy had been added, the reaction mixture was heated for 3–4 hours on the steam-bath with occasional shaking. The condenser was then set for downward distillation and the reaction mixture steam-distilled. From the steam-distillate was isolated 12 g. of *toluene*, b.p. 108–110°. The toluene was further identified by oxidation to benzoic acid, m.p. and mixed m.p. 121–122°. The steam-distillation residue was filtered, acidified, and extracted with ether. After evaporation of the ether a trace of material remained which did not give any reactions characteristic of a phenolic group and showed a negative qualitative sulfur test.

15. *Reduction of o-carboxyphenylthioglycolic acid. o*-Carboxyphenylthioglycolic acid was prepared from thiosalicylic acid and chloroacetic acid (32) Recrystallized from a mixture of alcohol and water, m.p. 212–214°; literature m.p. 210–211°.

Twenty grams of *o*-carboxyphenylthioglycolic acid was reduced in the usual manner with 100 g. of Raney alloy and 1500 cc. of 10% sodium hydroxide. After filtration, the alkaline solution was acidified, cooled, and filtered; yield 10.5 g., m.p. 121–122°, mixed m.p. with *benzoic acid* 122–123°; N.E., 122; Found: 123. In two experiments on the reduction of this compound, considerably less than the given amount of Raney alloy was used. In both of these experiments a large amount of the starting material was recovered along with 10–30% yields of benzoic acid. With the given amounts of alloy, none of the starting material was recovered, the crude reduction product giving a negative test for sulfur.

16. *Preparation and reduction of 3-methyl-6-benzylmercaptophenylglyoxylic acid.* To 1.78 g. (0.01 mole) of 5-methylthianaphthenequinone dissolved in 10 cc. of 20% potassium hydroxide and 10 cc. of alcohol there was added 3.5 g. of benzyl chloride. The reaction mixture became warm and within a few minutes was completely colorless. It was heated for ten minutes on the steam-bath, cooled, and extracted with ether. The aqueous solution was freed from ether, cooled, and acidified, yielding 2.6 g. of a yellow crystalline solid, m.p. 136–139°. Recrystallized from ethyl alcohol, m.p. 138.5–139.5°.

Anal. Calc'd for $C_{16}H_{14}O_3S$: C, 67.11; H, 4.93.
Found: C, 67.24; H, 4.96.

Five grams of the thioether was reduced in the usual manner with 15 g. of Raney alloy in 250 cc. of 10% sodium hydroxide. The reaction mixture was worked up in the usual manner; the residue from the ether extraction, after recrystallization from benzene-petroleum ether, gave 2 5 g. of colorless needles melting at 94–96°. A second recrystallization raised the melting point to 95–96°; N.E., 166; Found: 165 4. Mixed melting point with *m-methylmandelic acid* of experiment 8 showed no depression.

17. *Reduction of α-phenylmercapto-p-hydroxycinnamic acid.* Twenty grams of the cinnamic acid (12) was reduced with 50 g. of Raney alloy in 1000 cc. of 10% sodium hydroxide. The reduction was run under an efficient reflux condenser. After the reduction was complete, the solution was steam-distilled. From the steam-distillate *benzene* was isolated and identified by boiling point. The alkaline solution was filtered from the nickel, acidified to Congo Red with hydrochloric acid and exhaustively extracted with ether. The ether residue amounted to 10 g. and showed characteristic reactions for a hydroxyl and a carboxyl group. The residue was dissolved in ether and the ether solution extracted with sodium bicarbonate. The sodium bicarbonate solution on acidification and extraction with ether yielded a solid product which was identified as *β-(p-hydroxyphenyl)propionic acid,* m.p. and mixed m.p. 127–128°; N.E., 166; Found: N.E., 166.5.

18. *Reduction of α-phenylmercapto-β-(p-hydroxyphenyl)propionic acid.* Twenty grams of this acid (12) was reduced in exactly the same manner as described for the corresponding cinnamic acid. The steam-distillate yielded *benzene,* identified by b.p. and the steam-distillation residue, after acidification and extraction with ether, gave 8.9 g. of *β-(p-hydroxyphenyl)propionic acid,* m.p. and mixed m.p. 127–128°.

19. *Reduction of α-phenoxy-p-hydroxycinnamic acid.* Twenty-five grams of this acid (12) was reduced with 35 g. of Raney alloy in 700 cc. of 10% sodium hydroxide. After filtration of the nickel, the filtrate was added slowly to ice-cold hydrochloric acid. The acidified solution was thoroughly extracted with ether, the ether extracts combined, and then extracted with 5% sodium bicarbonate. The ether extracts on evaporation gave 1.2 g. of *phenol* identified by the m.p. of the aryloxy derivative, m.p. 98–99°. Mixed m.p. with an authentic sample of *phenoxyacetic acid* showed no depression.

The sodium bicarbonate extract was freed of ether, filtered through Supercel, and acidified. Upon extraction with ether and removal of the ether, a 6.4 g. residue was obtained which was identified as *β-(p-hydroxyphenyl)propionic acid;* m.p. and mixed m.p. 126.5–127°.

20. *Reduction of α-phenoxy-β-(p-hydroxyphenyl)propionic acid.* Twenty-five grams of this acid (12) was treated as described for the corresponding cinnamic acid. On acidification of the reduction filtrate, 14.6 g. of the starting material was obtained, m.p. and mixed m.p. 166–167°. The acidified filtrate was then extracted with ether and 1.6 g. of *β-(p-hydroxyphenyl)propionic acid* was obtained along with small amounts of *phenol.*

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SUMMARY

Organic sulfur compounds are hydrogenolyzed by the action of a nickel-aluminum alloy and aqueous alkali. In general, the reaction proceeds smoothly and good yields of desulfurized products are obtained.

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THE REACTION BETWEEN QUINONES AND METALLIC ENOLATES. XXII. NITROTRIMETHYLQUINONE AND SODIOMALONIC ESTER (1)[1]

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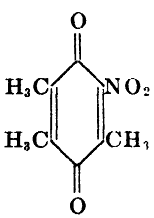
When a quinone possessing an unsubstituted position reacts with a metallic enolate, 1,4-addition occurs and the primary product is a hydroquinone. Fully substituted quinones lack the ability to yield, by addition of an enolate, an intermediate which can aromatize to a hydroquinone. When such quinones react with enolates, they do so either (a) by replacement, in which one of the substituents of the quinone is replaced by the enolate ion or (b) by condensation at a methyl group, with formation of a coumarin. With sufficient data available, it should be possible to predict whether a fully substituted quinone, substituted by a combination of methyl and replaceable groups, will react by replacement or by condensation at a methyl group. To extend and amplify the data so far available, nitrotrimethylquinone, (I), a quinone substituted by both methyl groups and the strongly electron-attracting nitro group, has been studied with respect to its behavior toward sodiomalonic ester.



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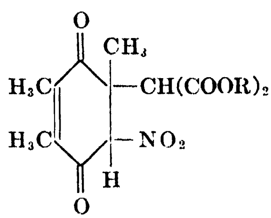

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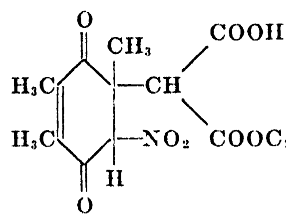
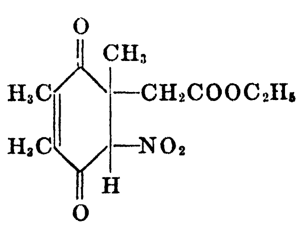
VII R = CH_3



III



IV

The quinone I and ethyl sodiomalonate reacted readily; a crystalline product $C_{16}H_{21}NO_8$ (II), was isolated in good yield from the reaction mixture after acidi-

[1] Abstracted from a thesis by Frank A. Cutler, Jr., presented to the Graduate Faculty of the University of Minnesota, in partial fulfillment of the requirements for the Ph.D. degree, April, 1948. N. R. C. Predoctoral Fellow, 1946–1948; present address: Merck and Co., Inc., Rahway, N. J.

fication. The composition of the product corresponds with that required for a substance derived by direct addition of the two components. The substance was almost white, although the crystals invariably showed a tinge of green; it decomposed on prolonged heating, but could be distilled at 190–200°/4.5 mm. with 80% recovery. The substance appeared to exist in two forms, one melting at about 80°, and the other at about 62°. Immediately after crystallization, the higher-melting form predominated; on standing, the solid changed, often very rapidly, until the lower-melting form predominated. During the transition, very wide ranges in the melting point were encountered, and it was not unusual for the crystalline mass to liquefy at room temperature, after which it solidified once more.

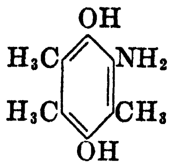
The substance did not dissolve immediately in aqueous sodium bicarbonate, or carbonate, but after standing in contact with either of these reagents for a day, a yellow solution resulted. In alcohol, the substance was sufficiently acidic to be titrated; one equivalent of alkali was required for neutralization. The substance was quite sensitive toward alkalis, but fairly stable toward cold mineral acids. When heated in ethanol or acetone, decomposition resulted. The substance did not decolorize a solution of bromine in carbon tetrachloride, but it rapidly decolorized neutral or alkaline permanganate although no significant amounts of crystalline oxidation products could be isolated. The substance was not a hydroquinone, for it was inert to the action of a solution of ferric sulfate; nor was there any reaction with acetic anhydride. No carbonyl derivatives were obtained by action of either phenylhydrazine or semicarbazide.

Although the substance was an ester, it was hydrolyzed to crystalline material only under carefully controlled conditions; when dissolved in ice-cold ammonium hydroxide and subjected to the action of a cold solution of potassium hydroxide in ammonium hydroxide, there was produced a gummy solid which gradually dissolved and then the solution, after acidification, produced an acid $C_{14}H_{17}NO_8$ (III) melting at 123.5–124.5° with evolution of carbon dioxide. The acid required two moles of alkali for neutralization; this, together with the composition of III and the behavior of II as a mono acid on titration, made it evident that hydrolysis of I had involved only one of the carbethoxyl groups.

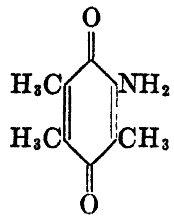
$$\underset{\text{II}}{C_{16}H_{21}NO_8} + H_2O \rightarrow \underset{\text{III}}{C_{14}H_{17}NO_8} + C_2H_5OH \rightarrow \underset{\text{IV}}{C_{13}H_{17}NO_6} + CO_2$$

When III was refluxed for a short time in xylene, decarboxylation occurred and a new acid IV, melting at 63–66°, was produced. Acid IV was a strong acid, requiring one mole of alkali for neutralization. The substance IV was attacked by ammoniacal potassium hydroxide solution, but the product could not be obtained pure.

When reduced by action of sodium hydrosulfite in ammonium hydroxide, II gave a white product (V) which rapidly became pink in the air and which, upon oxidation, gave a deep red quinone VI. For comparative purposes, nitrotrimethylquinone I was subjected to the same sequence of reactions; the results were



V R = H



VI

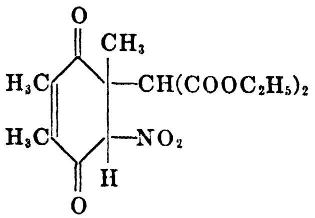
the same. The red quinone VI was obtained also by catalytic reduction of I, followed by oxidation of the hydroquinone.

When the addition product II was dissolved in ethanolic potassium hydroxide at room temperature, a bright yellow potassium salt soon separated. The analytical values given by this salt showed such a low content of carbon and hydrogen that no logical empirical formula could be deduced. The salt was readily soluble in water; acidification of the solution produced no precipitate until the solution was heated. The solid was nitrotrimethylquinone I; when the cold acidified solution of the salt was extracted with ether, only a resinous solid could be isolated from the extract. Control experiments with the quinone I paralleled the behavior of II; when I was dissolved in ethanolic potassium hydroxide, it decomposed and no I could be recovered after acidification of the solution. Likewise, when I was dissolved in ammonium hydroxide and the solution was acidified, no solid separated, nor could anything be removed from the solution by ether extraction. Yet, when the acidified solution was warmed, nitrotrimethylquinone separated.

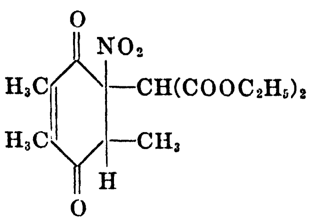
The experimental data were sufficient to establish the structure of the addition product as II. It was apparent from the several reactions of II, in which the quinone I was formed, that II must possess the skeletal structure of I, for these reactions, in effect, constituted a reversal of the initial reaction leading to II. Malonic ester was never isolated from any of these reaction products, though the odor of it was apparent. Saponification of one ester group in II and the ready decarboxylation of the product indicated that II was a malonic ester; the stability on distillation, and the slow rate of solution in carbonate, indicated absence of a carboxyl group in II. The origin of the acidity of II did not lie in the enolizable hydrogen atom of the malonic ester group, for IV was even stronger as an acid than was II; the acidity therefore lay in the nitro group, which must be so placed in II that an *aci*-salt could be formed.

Having established that the reaction between the malonate and the quinone I was a simple addition, there were *a priori* twelve structures which could be written for such a product. Four of these were derived by addition to the quinone as an α,β-unsaturated ketone; two by addition at the carbonyl group; three by addition to a "pentad enol" involving one of the methyl groups and leading to hydroquinones; two by 1,6-addition giving mono ethers of the hydroquinone; and one nitronic ester. The second, third, and fourth of these modes of addition would all lead to hydroxyl compounds, which the addition product was not; these

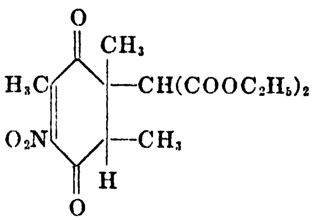
modes of addition and the resulting structures, were therefore eliminated. The fifth mode of addition would lead to a substituted methyl nitronic ester; Arndt and Rose (2) have shown that all known methyl nitronic esters decompose violently at 70–90°; the addition product II could be distilled without decomposition



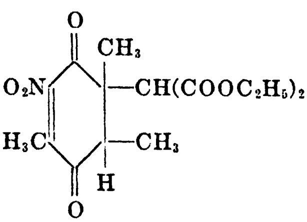
A = II



B



C



D

at 190–200°. There remained, therefore, to consider only the four structures derivable by the first mode of addition. Structures B, C, and D represent compounds which, either as such or in their enolic forms, would not be sufficiently acidic to be titratable. Structure A, however, represents the substance as a secondary nitro compound which would be quite acidic and titratable, as II was found to be. Hence, the most probable structure for II appeared to be A; using this structure, the other properties of II were readily understood. The melting point behavior of II indicated the existence of two forms, easily interconvertible. Structure A permits a *cis* and a *trans* form, easily interconvertible through the *aci* form of the secondary nitro compound. The fact that II was nearly colorless is not in disagreement with structure A, for the addition product of *p*-xyloquinone and 1,3-cyclohexadiene, having a structure very much like A, is colorless (3). The ready reversal of the reaction by which II is formed is best interpreted in terms of structure A: the acidic proton is easily removed from the carbon atom holding the nitro group, and the resulting anion would be expected to undergo readily a cleavage into nitrotrimethylquinone and the anion of malonic ester.

In its behavior toward sodiomalonic ester, the quinone I behaved as a nitroolefin; the reaction demonstrates the strong resonance effect (electron-attracting) of the nitro group, and is completely analogous to the reaction between β-nitrostyrene and methyl sodiomalonate studied by Kohler and Engelbrecht (4), and the product of this reaction shows certain similarities with II—thus the nitromalonic ester obtained by Kohler and Engelbrecht could not be hydrolyzed to the

corresponding acid; action of alkalis produced only oily decomposition products, and action of acids resulted in loss of the nitro group.

The behavior of nitrotrimethylquinone was studied toward three other enolates. From ethyl sodioacetoacetate, no crystalline product could be isolated and only traces of the quinone were recovered. From the bromomagnesium enolate of acetomesitylene, only oils and resins resulted. From methyl sodiomalanate, however, a crystalline addition product VII was obtained. This substance was, in its behavior, completely analogous with II.

The results of this work show that, in addition to replacement and condensation at a methyl group, a completely substituted quinone may react with an enolate by direct addition, and that steric hindrance plays a comparatively minor role in the reaction of quinones with enolates.

EXPERIMENTAL[2]

Nitrotrimethylquinone (I). Trimethylquinone (5) (30 g.) was dissolved in a mixture of nitric acid (90 cc.) and sulfuric acid (30 cc.) and the solution was heated to 60°. After ten to twenty minutes, two layers formed; the temperature was raised to 65° for twenty minutes, when the lower layer became clear. Control of the temperature was important, for the reaction sometimes became violent, with copious evolution of oxides of nitrogen. The solution was poured into a mixture of ice (1 kg.) and water (1000 cc.). The yellow solid from three experiments was combined, pressed dry, and while still cold was dissolved in nitric acid (200 cc.) and the solution was brought to 80° for five minutes; this converted any unchanged trimethylquinone into the nitroquinone. The solution was poured into ice-water as before, and the mixture was allowed to come to room temperature. The solid was removed, allowed to stand in the air for several days until dry, and then crystallized twice from 800-cc. portions of petroleum ether (b.p. 90–100°). The bright yellow nitroquinone I weighed 70 g. (60%) and melted at 107 5–110.5°. This product was pure enough for use in the subsequent reactions; the pure quinone, m.p. 113–114°, could be obtained by adding water gradually to a warm solution of the substance in ethanol. It was important not to boil the ethanolic solution, for this resulted in production of highly colored by-products, one of which, a red compound, melted at 133.5–135.5°. The melting point of the nitroquinone, recorded in the literature, is 112–113° (6, 7). Nitrotrimethylquinone was destroyed by action of cold ethanolic potassium hydroxide or of potassium hydroxide in ammonium hydroxide. The quinone formed a yellow solution in dilute ammonium hydroxide. When this solution was acidified, no solid separated, nor could anything be removed by ether extraction, but when the yellow acidified solution was heated briefly and then cooled, nitrotrimethylquinone separated in yellow plates. Nitrotrimethylquinone could not be titrated in ethanol because of the intense colors formed as soon as any base was added.

2-Nitro-3-(dicarbethoxymethyl)-3,5,6-trimethylcyclohexene-5-dione-1,4 (II). A solution of ethyl sodiomalonate was prepared by refluxing ethyl malonate (40 g., 0.25 mole) in dry, peroxide-free dioxane (8) (80 cc.) with sodium (5.06 g., 0.22 mole) for one and three-fourths hours. The solution was cooled and added slowly to a solution of the nitroquinone I (19.5 g., 0.1 mole) in dioxane (150 cc.) maintained at 19–21°. The reaction was exothermic; twenty minutes was required for addition of the first half of the enolate, during which the color became red. As soon as half of the enolate was added, the color of the solution became an intense deep red, and no further evolution of heat occurred. The second half of the enolate was added rapidly, and the mixture was allowed to stand for sixteen hours. The solution was poured into ice and hydrochloric acid (100 cc.), the orange oil was removed and

[2] Microanalyses by R. W. Amidon, Jay S. Buckley, J. R. Kerns, and S. A. Sundet.

dissolved in ethanol (95%, 100 cc.) at room temperature. Water was added dropwise, with occasional cooling, until crystallization was induced. The product was removed, washed with cold ethanol until nearly white, and the combined filtrates and washings were further diluted with water as before. This process was repeated several times until no further crystallization occurred. Since the product frequently liquefied on standing, all the solids were combined after a brief drying period, and crystallized from petroleum ether (200 cc., b.p. 90–100°). In this way there was obtained 26.6 g. (75%) of nearly white material, melting over various ranges within the limits 58–78°. The substance II crystallized readily from petroleum ether (b.p. 90–100°) in the form of stubby prisms terminated at each end by a pair of oblique planes; the crystals always had a faint greenish cast. Immediately after crystallization, the substance usually melted at 68–78°, occasionally as high as 81°. On standing, the crystals became translucent, and the substance was transformed into the lower-melting form. The rate of this change varied greatly with different preparations; one specimen did not change over a period of two years, another, after two weeks, melted at 61–62.5°. When the material was finely divided, the change could often be brought about by rubbing or stirring, in which case the entire mass liquefied and then resolidified to the form melting at 57–62°. Recrystallization from petroleum ether again gave the high-melting form, and the cycle could be repeated indefinitely. When crystallized from ethanol, the product changed rapidly to the lower-melting form, *via* the liquid. Because of this peculiar behavior, it was difficult to obtain analytical specimens free from solvent

Anal Calc'd for $C_{16}H_{21}NO_8$: C, 54 08; H, 5.96; N, 3.94, Mol wt , 355.3; Neut. equiv. (one), 355.3.

Found: C, 54 48, 55.25, 56 37; H, 5 68, 5.96, 6.97; N, 3 81; Mol wt. (benzene, cryoscopic), 332; Neut. equiv. 377, 383.

The following *variants* in procedure were tried, with no improvement and usually a decrease in yield and quality of product: reduction of the reaction time to two hours; termination of the reaction when half the enolate had been added; provision of a nitrogen atmosphere; substitution of benzene or ethanol for dioxane. Reversal of the order of adding the solutions had no effect one way or another. Substance II, regardless of its melting point, formed yellow solutions slowly (one day) in contact with aqueous sodium bicarbonate (5%) or carbonate (10%); II was readily soluble in ammonium hydroxide. In ethanol, II could be titrated to a neutral equivalent of 377–383 using phenolphthalein as the indicator Some specimens of II became orange on prolonged standing, particularly at the point of contact of glass and sample. The substance was not stable on prolonged heating, but it could be rapidly distilled at 190–200°/4.5 mm. giving an orange distillate which, crystallized from petroleum ether, gave the solid form melting at 67–80° (80% recovery). Solutions of II in ethanol or acetone, when heated, became orange or red, and II could be recovered from these solutions only in poor yield, if at all. No acetate resulted when II was subjected to the action of acetic anhydride and sulfuric acid; from 1 g. of II, 0.6 g. was recovered, and the remainder of the product was a black tar. Oxidation of II (1.0 g.) by action of ferric sulfate produced no quinone; the only product (0.13 g.) was unchanged II. No phenylhydrazone could be isolated when II was subjected to the action of phenylhydrazine; the only product was a red oil. Nor could any semicarbazone be obtained. A solution of bromine in carbon tetrachloride did not react with II. Aqueous potassium permanganate, when added to a solution of II in acetone, was rapidly decolorized, but no oxidative degradation products could be isolated in quantity sufficient for identification. Many attempts were made to hydrolyze II under acidic conditions, but these experiments led either to unchanged material, or to intractable oils.

Potassium salt. Potassium hydroxide (15 g.) was dissolved in ethanol (95%, 100 cc.); the solution was filtered to remove carbonates and the filtrate was cooled. To it was added solid II (5 g); the flask was stoppered and shaken until solution was complete. The yellow potassium salt soon separated; after one and one-half hours it was removed and washed with ethanol and ether. The first crop weighed 4.2 g.; the filtrate, on standing, deposited a second crop of 0.66 g. The substance was dissolved in water, the solution was

filtered, and the filtrate was poured into ethanol. The solid was removed, washed with alcohol and ether, and dried in a vacuum desiccator over calcium chloride. No logical formula could be calculated from the analytical values.

Anal. Found: C, 28.35; H, 3.41; K, 26.13, 25.89.

An aqueous solution of the salt (0.5 g.) acidified with hydrochloric acid and warmed briefly, deposited nitrotrimethylquinone (0.015 g.) on cooling. No other material could be isolated; in many experiments, the yield of quinone never exceeded 10%. If, instead of heating the acidified solution, it was extracted with ether, an amorphous resin was found in the ether extract. An aqueous solution of the resin, when heated, produced traces of nitrotrimethylquinone.

2-Nitro-3-(carboxycarbethoxymethyl)-3,5,6-trimethylcyclohexene-5-dione-1,4 (III). The addition product II (10 g.) was dissolved in concentrated ammonium hydroxide (50 cc.) and to the chilled solution there was added a cold solution of potassium hydroxide (20 g.) in ammonium hydroxide (50 cc.). An orange solid separated; this gradually redissolved. The mixture was cooled (0°) and stirred for one hour, and then poured slowly into a mixture of ice (600 g.) and hydrochloric acid (200 cc.). The solid was removed, triturated with water (75 cc.), filtered, and dried. It weighed 6.08 g. (66%) and melted at 120.5–121° (dec.). It could not be crystallized from organic solvents; for purification it was dissolved in dilute aqueous sodium bicarbonate and the solution was filtered into a well stirred mixture of ice and hydrochloric acid. This process was repeated several times, resulting in a product melting at 123.5–124.5° with darkening and evolution of gas. The gas was identified as carbon dioxide.

Anal. Calc'd for $C_{14}H_{17}NO_8$: C, 51.37; H, 5.24; Neut. equiv. (two) 163.6.
Found: C, 51.19; H, 5.25; Neut. equiv., 164, 165.

The experimental conditions as outlined above must be followed closely with respect to time, temperature, reagents and order in which the reagents were combined. When II was refluxed with aqueous sodium hydroxide (5%) the solution became very dark and only a red oil could be obtained upon acidification.

2-Nitro-3-(carbethoxymethyl)-3,5,6-trimethylcyclohexene-5-dione-1,4 (IV). Compound III (10 g.) was dissolved in hot xylene (200 cc.) and the solution was refluxed (132°) for twenty minutes. The cooled solution was extracted with six 50-cc. portions of aqueous sodium carbonate (10%), which were slowly added to ice-cold hydrochloric acid (100 cc.). The yellow solid was removed, washed with water, and dried; it weighed 4.85 g. and melted at 62–64.5°. The xylene layer was evaporated under reduced pressure and the residue was dissolved in ether and extracted with carbonate; acidification of the carbonate extracts yielded a further 1.15 g. of material melting at 62–66°. Evaporation of the ether yielded 0.06 g. of nitrotrimethylquinone. The total product (6 g., 70%) was crystallized twice from small amounts of ethanol (95%), when it formed light greenish-yellow microcrystals melting at 63–66°.

Anal. Calc'd for $C_{13}H_{17}NO_6$: C, 55.11; H, 6.05; Neut. equiv. (one) 283.3.
Found: C, 55.32; H, 6.01; Neut. equiv., 283.

Substance IV could not be obtained from III by simple heating. At 120–130° for twelve minutes, 0.79 g. of II lost 0.082 g. in weight (theoretical, 0.107 g.). No crystalline material could be isolated from the dark residue. A sample of III was distilled under 5 mm. pressure, with a bath temperature of 195°. The only pure material isolated from the distillate was a trace of nitrotrimethylquinone. Attempts to hydrolyze IV (2.0 g.) by the procedure used for hydrolysis of II led to a yellow solid (1.85 g.) melting with decomposition at 98–139°, and from which no pure material could be isolated.

Reduction of II. A. Sodium hydrosulfite (2.9 g.) was added in small portions, with gentle warming, to a solution of II (1 g.) in ammonium hydroxide (10 cc.). Ethanol (5 cc.) and water (5–10 cc.) were added during the reduction. The solution became colorless and the white, fibrous crystals of aminotrimethylhydroquinone deposited. The mixture was cooled, the solid (0.3 g., 62%) was removed, dissolved in ethanol and the solution was

added to a solution of ferric chloride. The red solid (0.2 g.) was removed; it melted at 169–170.5° alone or when mixed with authentic aminotrimethylquinone.

B. A solution of II (6.78 g.) in benzene (20 cc., thiophene-free) was shaken with hydrogen (30 lb.) in the presence of platinum oxide catalyst (0.1 g.). The solids were removed, extracted with acetone, and the extract was added to ferric chloride as above. There resulted 0.33 g. of aminotrimethylquinone, melting at 168–170.5°.

2-Nitro-3-(dicarbomethoxymethyl)-3,5,6-trimethylcyclohexene-5-dione-1,4 (*VII*). The reaction between nitrotrimethylquinone (1.95 g.) and methyl sodiomalonate was carried out essentially as described above for the preparation of II. The product (1.1 g., 34%), recrystallized from benzene, formed prisms which softened at 105° and melted at 109–114°.

Anal. Calc'd for $C_{14}H_{17}NO_8$: C, 51.37; H, 5.24; N, 4.28.

Found: C, 51.74; 52.44; H, 5.71, 5.36; N, 4.26.

When *ethyl sodioacetoacetate* was substituted for the malonate in the above experiment, the product was a dark red oil from which a small amount of nitrotrimethylquinone could be isolated as the only solid product. A similar result was obtained when the reaction was carried out in ethanol as the solvent.

Acetomesitylene (5 g., 0.03 mole) was added to a solution of ethylmagnesium bromide (from ethyl bromide, 2.25 cc., magnesium, 0.75 g., and ether, 30 cc.). To the resulting suspension of the enolate of acetomesitylene, there was added dropwise (thirty minutes) and with stirring, a solution of nitrotrimethylquinone (2.9 g.) in ether (80 cc.). A brown solid separated; the mixture was gently refluxed for three hours and allowed to stand for a day, after which it was poured into iced hydrochloric acid (10 cc.) and extracted with ether. The combined extracts were washed with water, the solvent was removed, and the residue was extracted with petroleum ether (b.p. 28–38°) to remove acetomesitylene. There remained an amorphous, orange material (1.44 g.) from which no pure material could be obtained.

SUMMARY

In the reaction between nitrotrimethylquinone and methyl or ethyl sodiomalonate, the nitroquinone behaves as an α,β-unsaturated nitroolefin; addition of the enolate occurs directly to a double bond of the quinone without elimination of any group. This type of reaction between a fully substituted quinone and a metallic enolate is new, and the reaction demonstrates the strong resonance effect (electron attraction) of the nitro group.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

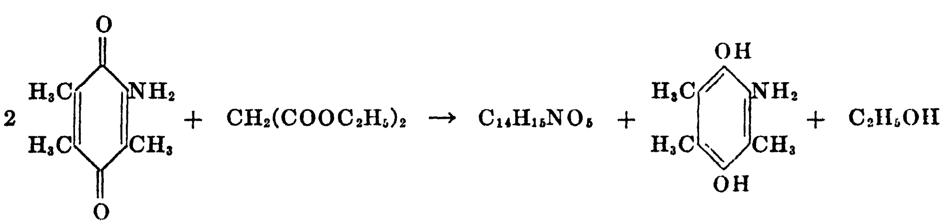
THE REACTION BETWEEN QUINONES AND METALLIC ENOLATES. XXIII. AMINOTRIMETHYLQUINONE AND SODIOMALONIC ESTER (1)[1]

LEE IRVIN SMITH AND FRANK A. CUTLER, JR.

Received, January 27, 1949

In the previous paper (1) the behavior of nitrotrimethylquinone toward sodiomalonic ester was described. In this paper, a similar study of aminotrimethylquinone is presented; the study was undertaken because of the strongly contrasting electronic character of the nitro and amino groups in the two quinones, and in order to extend the data regarding the several reactions which may occur between a quinone and a metallic enolate.

The quinone I and sodiomalonic ester reacted in dioxane to form a deep red solid which, when acidified, produced an orange solid $C_{14}H_{15}NO_5$ (II). The composition of II corresponded to a product formed from one mole each of II and ethyl malonate, with elimination of ethanol and two hydrogen atoms, and indicated strongly that II was a coumarin derivative. Neither the quinone I nor its hydroquinone was isolated by steam-distillation of the dioxane filtrates; the only material isolated from the steam-distillate was a small amount of hydroxytrimethylquinone. In a control experiment, it was found that the quinone I, when steam-distilled from dilute acid, was largely converted into hydroxytrimethylquinone. It thus appeared that the reaction was analogous to that between duroquinone and sodiomalonic ester (2) and that the enolate anion had attacked the quinone I at a methyl group.

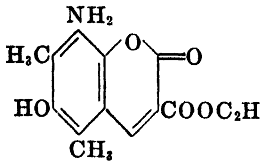


I II

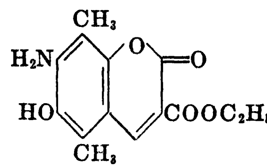
Three coumarins, A, B, and C, were possible products of this reaction, depending upon which of the three methyl groups in I had been attacked. In addition, attack at the methyl group *ortho* to the amino group could give rise to the carbostyril D by a cyclization involving the amino group.

The substance II was soluble in concentrated acid, but insoluble in dilute acid; the Folin (phenol) test was positive, and action of ferric chloride produced colored oxidation products. These properties indicated that II was a 6-hydroxy-

[1] Abstracted from a thesis by Frank A. Cutler, Jr., presented to the Graduate Faculty of the University of Minnesota, in partial fulfillment of the requirements for the Ph.D. degree, April, 1948.



A



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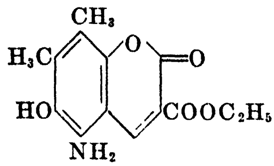

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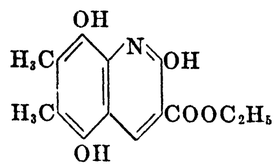
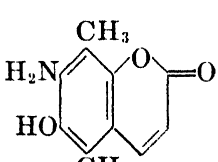


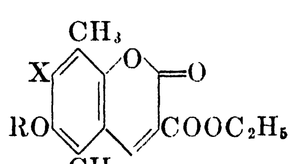
D

coumarin; when it was found that II could be diazotized, the presence of an amino group was demonstrated and structure D, the carbostyril, was eliminated as a possibility.

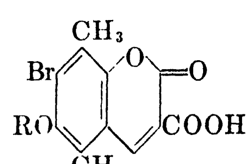
The coumarin II formed a monoacetyl derivative (III) and a colorless diacetyl derivative (IV). The monoacetyl derivative III gave a positive Folin test; III was therefore the N-acetyl derivative. The diacetyl derivative IV gave no Folin test; it was therefore the O,N-diacetyl compound. When II was refluxed in hydrochloric acid, hydrolysis and decarboxylation occurred; the initial product separating from the acid solution appeared to be an amine hydrochloride but this was readily hydrolyzed in water to give V. The rather easy decarboxylation of the coumarin II was unusual, for the other 3-carboxycoumarins studied so far in this series undergo decarboxylation only under severe conditions. For this reason, it is probable that decarboxylation of II involved opening of the heterocyclic ring, with decarboxylation followed by recyclization.



V



VI X = Br; R = H
VII X = Cl; R = H
VIII X = Br; R = Ac



IX R = H
X R = Ac

Two of the three bromine analogs of A, B, and C (NH_2 replaced by Br) namely, the analogs of A and C, were known (3). The simplest proof of structure of II was to convert II into the bromine analog *via* the Sandmeyer reaction. In this way, II was converted, in 80% yield, into a bromocoumarin VI and in 65% yield into a chlorocoumarin VII. The bromocoumarin VI was obtained in three polymorphic forms, melting at 151–153°, 158–159.5°, and 160.5–162°, respectively; it formed an acetate VIII, melting at 160–161°. Hydrolysis of the bromocoumarin ester VI yielded an acid IX, melting at 250.5–251.5° (dec.) which

formed an acetate X melting at 219.5–220.5°. It was obvious that II did not possess structure A; although the melting points of the respective bromo derivatives of C and II were quite different, the melting points of the other derivatives were close. However, the mixed melting points of the derivatives of C and II were in every case depressed and it became apparent that II must be represented by structure B and that the bromo analog derived from II must have the analogous structure, namely, 3-carbethoxy-5,8-dimethyl-6-hydroxy-7-bromocoumarin VI.

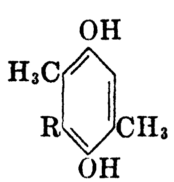
This was confirmed by an independent synthesis of VI. *p*-Xylohydroquinone XI was converted by bromination into the monobromohydroquinone XII and the latter was chloromethylated to form the benzyl chloride XIII. When XIII was subjected to the action of ethyl sodiomalonate, alkylation, cyclization and dehydrogenation occurred, producing VI. This specimen of VI showed the same triple melting point as the specimen obtained from II; the ester acetate, acid,

TABLE I

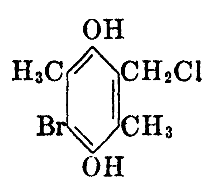
MELTING POINTS OF BROMINE ANALOGS °C.

RELATED AMINE	COUMARIN ESTER	ACETATE OF ESTER	COUMARIN ACID	ACETATE OF ACID
A	206–207			
C	200	160–161	250	223
II Trimorphic	151–153 158–159.5 160.5–162	160–161	250.5–251.5	219.5–220.5

and acid acetate all had the same melting points as those derived from II; melting points of mixtures of the respective derivatives were not depressed.



XI R = H
XII R = Br



XIII

Hence, when aminotrimethylquinone reacts with sodiomalonic ester, the product is a coumarin (B) resulting from attack of the enolate ion at the methyl group *para* to the amino group. As the yield of II (97.4% or 48.7% conversion) was high, it is unlikely that any other reaction occurred. The course of this reaction is interesting; it reflects the strong resonance effect (electron release) of the amino group. This reaction is in contrast with the behavior of bromotrimethylquinone—although the bromoquinone is converted into a coumarin, it is the methyl group *ortho* to the bromine atom which is involved.

EXPERIMENTAL[2]

Aminotrimethylquinone I. Nitrotrimethylquinone (1) (10 g.) dissolved in acetic acid (60 cc.) was shaken for three hours with hydrogen (30 lbs.) in the presence of platinum oxide catalyst (0.15 g.). The solution was filtered, acetic acid (50 cc.) was added to the filtrate, and air was drawn through the solution for two hours. The intensely red solution was chilled and neutralized with ammonium hydroxide, and the red solid was removed, washed with cold water, and dried. The dried product from two such experiments was extracted with benzene (175 cc.) in a Soxhlet extractor; from the extract, on cooling, there separated 12.32 g. (73%) of the aminoquinone melting at 166.5–170.5°. This was pure enough for condensation with malonic ester. A specimen, recrystallized from benzene, melted at 169.5–171.5°.

Anal. Calc'd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48.
Found: C, 65.51; H, 6.76; N, 8.33.

Aminotrimethylhydroquinone. The nitroquinone (1 g.), dissolved in acetone (10 cc.) and water (10 cc.), was heated and sodium hydrosulfite (4.2 g.) was added in small portions. As the acetone evaporated from the solution, water was added to keep the volume constant. The mixture was cooled and the white solid (0.61 g., 71%) was removed and dried. The hydroquinone melted with decomposition. When the melting point was determined in the ordinary way, the substance became red and melted at about 170°, the melting point of the quinone. In a bath preheated to 206°, the hydroquinone melted slowly; in a bath at 210°, it melted rapidly—hence the melting point was about 206–210°. The substance could be recrystallized from large volumes of hot water if sodium hydrosulfite was added. On exposure to air, the white solid soon became red; under nitrogen, it appeared to be stable. The hydroquinone (0.61 g.), dissolved in aqueous acetone, was oxidized by action of ferric chloride to the quinone, m.p., 166–171°. *Acetylaminotrimethylhydroquinone diacetate* was prepared from the crude hydroquinone by action of acetic anhydride containing a little sulfuric acid. Crystallized from ethanol (Norit), it was white and melted at 131–132.5°.

Anal. Calc'd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53.
Found: C, 61.22; H, 6.44.

Hydroxytrimethylhydroquinone. The aminoquinone I (0.37 g.) was dissolved in hydrochloric acid (10 cc.), the solution was diluted with water and the resulting suspension of aminoquinone was steam-distilled. From the cooled distillate (200 cc.), the hydroxyquinone (0.21 g., 57%) separated as orange needles melting at 94–95°.

Anal. Calc'd for $C_9H_{10}O_3$: C, 65.05; H, 6.07.
Found: C, 65.10; H, 6.19.

3-Carbethoxy-5,8-dimethyl-6-hydroxy-7-aminocoumarin (II = B). Ethyl malonate (29.9 g., 0.187 mole) in dry, peroxide-free dioxane (60 cc.) was refluxed with sodium (3.78 g., 0.164 g. atom) for one hour and the cooled solution of the enolate was added to aminotrimethylquinone (12.32 g., 0.75 mole) in dioxane (180 cc.). The mixture was protected from moisture by a calcium chloride tube, was stirred for seven hours, and then was allowed to stand for sixteen hours. The deep red solid was removed, washed with a little dioxane, and added to hydrochloric acid (1.2 *N*., 500 cc.). The yellow solid was removed and crystallized from ethanol (95%, 450 cc.), when it formed orange prisms (10.1 g., 97.4%) melting at 228–229°.

Anal. Calc'd for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05.
Found: C, 60.50; H, 5.50; N, 5.41.

The filtrate from the dark solid, exposed to air for two months, deposited a further amount of dark solid which was converted, by action of hydrochloric acid, into additional II (1.31 g.). Steam-distillation of the filtrate yielded a small amount of hydroxytrimethylquinone, m.p. and mixed m.p. 93.5–95°. The aminocoumarin ester II was sparingly soluble

[2] Microanalyses by R. W. Amidon and Jay S. Buckley, Jr.

in hot benzene; the solution in benzene or acetone showed a strong blue fluorescence. The compound was insoluble in 1.2 *N* hydrochloric acid, but dissolved in 6 *N* acid. Action of alkalis gave rise or orange or deep red colors which were not discharged when the solutions were shaken with sodium hydrosulfite. The Folin test was positive, and the substance was oxidized by permanganate. Action of ferric chloride upon an acetone solution of II (0.5 g.) gave rise to a deep red solution from which two solids were isolated: one of these was yellow (0.1 g.) and melted with decomposition at 300–325°; the other (0.05 g.) was dark red and decomposed at 187–191°. These substances were not investigated further.

3-Carbethoxy-5,8-dimethyl-6-hydroxy-7-acetylaminocoumarin (*III*). The aminocoumarin II (0.1 g.) was suspended in acetic anhydride (5 cc.). Sulfuric acid (2 drops) was added; the solid rapidly dissolved. The solution was allowed to stand for ten minutes, then was poured into water (20 cc.), neutralized with ammonium hydroxide, and the solid was removed and crystallized from ethanol (95%, 15 cc.). It weighed 0.097 g. (84%), melted at 256° (dec.) (bath preheated to 250°), and gave a positive Folin test.

Anal. Calc'd for $C_{16}H_{17}NO_6$: C, 60.18; H, 5.37; N, 4.39.
Found: C, 59.71; H, 5.60; N, 4.26.

3-Carbethoxy-5,8-dimethyl-6-acetoxy-7-acetylaminocoumarin (*IV*). Acetylation of II was carried out as above, except that the solution was allowed to stand for a week at room temperature before the product was isolated. The solid was dissolved in petroleum ether (150 cc., b.p. 90–100°), the solution was filtered to remove a small amount of III and the filtrate was cooled. The white solid (0.1 g., 76%) melted at 130.5–131.5° after it was crystallized twice from petroleum ether. The Folin test was negative.

Anal. Calc'd for $C_{18}H_{19}NO_7$: C, 59.83; H, 5.30.
Found: C, 59.87; H, 5.53.

5,8-Dimethyl-6-hydroxy-7-aminocoumarin (*V*). The coumarin ester II (2 g.) was refluxed for two hours in hydrochloric acid (6 *N*, 80 cc.). The mixture was cooled and the solid was removed and dried in a vacuum desiccator over potassium hydroxide. The material then weighed 1.62 g. (theoretical for $C_{11}H_{11}NO_3 \cdot HCl$, 1.74 g.) and did not melt below 265°. When added to water, the solid became bright greenish-yellow and the water contained chloride ion; the solution decomposed sodium bicarbonate with effervescence. This hydrochloride (from 0.5 g. of II) was dissolved in boiling water (300 cc.) and the solution was cooled. The solid (0.262 g., 71%) was dissolved in wet acetone and reprecipitated by addition of water, when it melted at 261° with decomposition. The substance was insoluble in aqueous sodium bicarbonate (5%).

Anal. Calc'd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40.
Found: C, 64.71; H, 5.68.

3-Carbethoxy-5,8-dimethyl-6-hydroxy-7-chlorocoumarin (*VII*). The aminocoumarin II (0.5 g., 0.002 mole) was dissolved in hydrochloric acid (10 cc.) and the cold solution was diazotized by dropwise addition of a solution of sodium nitrite (0.13 g., 0.002 mole) in water (5 cc.). A solution of cupric sulfate (2 g.) in water (10 cc.) was added and the mixture was heated on the steam-bath. The tan solid (0.35 g., 65%, m.p. 166–168°) was removed and crystallized three times from aqueous ethanol. It formed greenish needles which sintered at 166.5° and melted to a brown liquid at 171.5–173°.

Anal. Calc'd for $C_{14}H_{13}ClO_5$: C, 56.67; H, 4.41.
Found: C, 56.87; H, 4.70.

3-Carbethoxy-5,8-dimethyl-6-hydroxy-7-bromocoumarin (*VI*). The aminocoumarin VI (2 g., 0.007 mole) dissolved in hydrobromic acid (40 cc., 34%) was cooled (1°) and diazotized by dropwise addition (twenty minutes) of a solution of sodium nitrite (0.51 g., 97%, 0.007 mole) in water (10 cc.). Cuprous bromide (from 38.8 g. of cupric sulfate) was dissolved in hydrobromic acid (38 cc., 34%); the solution was cooled (1°) and added to the diazonium solution. The black solution was warmed gradually (thirty minutes) to 52°; the solid was removed, and the filtrate was heated to 75°. The combined solids were dissolved in ethanol (65 cc., 95%), the solution was filtered, the hot filtrate was diluted gradually with water (35 cc.) until solid began to separate, and cooled. The crude product (2 g., 81%) melted

partially at 148–152° and completely at 160–161°. The material, crystallized three times from dilute ethanol, as above, and dried at 100°, melted at 151–153°; the cooled melt remelted at 151–153°, 158–159.5°, or at 160.5–162°, depending upon whichever crystalline form first appeared when the melt was cooled. The melting points were distinct and reproducible. The low-melting form of VI occurred as stubby prisms; the form with intermediate melting point occurred as coarse needles, and the high-melting form occurred as fine fibres. The trimorphism was encountered in all specimens of VI.

Anal. Calc'd for $C_{14}H_{13}BrO_5$: C, 49.27; H, 3.84.
Found: C, 49.50; H, 3.89.

3-Carbethoxy-5,8-dimethyl-6-acetoxy-7-bromocoumarin (VIII). The bromocoumarin VI (0.1 g.) was warmed for thirty minutes in acetic anhydride (6 cc.) containing a drop of sulfuric acid. Water was added, the solid (0.096 g., 87%, m.p. 159–161°) was removed and crystallized three times from aqueous ethanol (50%), when it was white and melted at 160–161°.

Anal. Calc'd for $C_{16}H_{15}BrO_6$: C, 50.15; H, 3.95.
Found: C, 50.36; H, 3.90.

A mixture of VIII and 3-carbethoxy-6-acetoxy-7,8-dimethyl-5-bromocoumarin, m.p. 159–160° (3), melted at 154–156°.

3-Carboxy-5,8-dimethyl-6-hydroxy-7-bromocoumarin (IX). The bromocoumarin II (0.5 g.), heated on the steam-bath with hydrochloric acid (45 cc.) for one and three-fourths hours, gradually dissolved and then the solution deposited a solid. The product was removed from the cooled suspension and crystallized from benzene (130 cc.) when it formed dark yellow crystals (0.34 g., 74%) melting at 247.5–250.5° with decomposition (bath preheated to 244°). Recrystallized from benzene (Norit), the substance softened at 247° and melted at 250.5–251.5° (dec.) (bath preheated to 244°). The substance was readily soluble in aqueous sodium bicarbonate (5%).

Anal. Calc'd for $C_{12}H_9BrO_5$: C, 46.03; H, 2.90.
Found: C, 46.52; H, 2.90.

3-Carboxy-5,8-dimethyl-6-acetoxy-7-bromocoumarin (X). The coumarin IX (0.136 g.) was acetylated as described for VI. The product (0.135 g., 88%), crystallized three times from aqueous ethanol (Norit), was white and melted at 219.5–220.5°.

Anal. Calc'd for $C_{14}H_{11}BrO_6$: C, 47.34; H, 3.12.
Found: C, 47.28; H, 3.18.

A mixture of X and 3-carboxy-6-acetoxy-7,8-dimethyl-5-bromocoumarin, m.p. 220–225° (3) melted at 196–206°.

p-Xyloquinone was prepared from *p*-xylenol (4, 5) and reduced to the *hydroquinone XI* by the method of Smith and Johnson (6). The hydroquinone melted at 210–213.5°.

Bromo-p-xylohydroquinone (XII). A solution of *p*-xylohydroquinone XI (6.35 g., 0.046 mole) in acetic acid (330 cc.) was stirred and brominated at room temperature by gradual (one hour) addition of a solution of bromine (7.2 g., 0.045 mole) in acetic acid (20 cc.). The mixture was stirred for three hours, allowed to stand for seventeen hours; then concentrated to 25 cc. under reduced pressure and with exclusion of air. The solution was diluted to 100 cc. by dropwise addition of water; the mixture was chilled and the solid was removed and crystallized from petroleum ether (450 cc., b.p., 90–100°). The white needles (6.5 g., 66%) melted at 123–126.5° with darkening.

Anal. Calc'd for $C_8H_9BrO_2$: C, 44.26; H, 4.18.
Found: C, 44.61; H, 4.60.

The *diacetate*, prepared in the usual way and crystallized from aqueous ethanol, melted at 107.5–109°.

Anal. Calc'd for $C_{12}H_{13}BrO_4$: C, 47.86; H, 4.35.
Found: C, 47.72; H, 4.50.

2,5-Dimethyl-3,6-dihydroxy-4-bromobenzyl chloride (XIII). The hydroquinone XII (3 g.) was dissolved in acetic acid (60 cc.) containing formalin (6 cc., 40%), and the solution was maintained at 5–15° while a brisk stream of hydrogen chloride was passed into it for three

and one-half hours. The solid was removed, washed with cold water, dried, and crystallized from benzene (35 cc.). It was cream-colored, weighed 1.75 g. (50%), and melted at 147–150°. The analytical specimen, crystallized three times from benzene, was white and melted at 147.5–150°.

Anal. Calc'd for $C_9H_{10}BrClO_2$: C, 40.71; H, 3.80.

Found: C, 40.90; H, 3.95.

A solution of the benzoyl chloride XIII (0.8 g., 0.003 mole) in dry, peroxide-free dioxane (10 cc.) was added, dropwise (twenty minutes), and with stirring, to a solution of sodiomalonic ester (from sodium, 0.21 g., ethyl malonate, 1.82 cc.) in dioxane (5 cc.). The mixture was stirred for seven hours and then allowed to stand for seventeen hours. The deep red solid was removed, washed with a little dioxane, and added to hydrochloric acid (1.2 *N*., 10 cc.). The yellow solid, crystallized from aqueous ethanol, weighed 0.22 g. (22%) and melted at 148–151.5° with sintering at 145.5°. Recrystallized from dilute ethanol and dried at 100°, the solid sintered at 150° and melted at 151–153°. The cooled melt remelted at 151–153°, 158–159.5°, and 160.5–162°. A mixture of this material and the bromocoumarin obtained from the aminocoumarin II showed the same melting points. Acetylation of this product gave an acetyl derivative melting at 159–161°, alone or when mixed with VIII; hydrolysis of the product by action of hydrochloric acid gave an acid melting at 247.5–250.5°, alone or when mixed with IX; acetylation of the acid gave an acetyl derivative melting at 214–217°, alone or when mixed with X.

SUMMARY

1. Aminotrimethylquinone has been synthesized.

2. This quinone reacts with sodiomalonic ester to form 3-carbethoxy-5,8-dimethyl-6-hydroxy-7-aminocoumarin (II = B) by attack of the enolate anion at the methyl group of the quinone *para* to the amino group, demonstrating the strong resonance effect (electron release) of the amino group in this quinone.

3. The chemical properties of the aminocoumarin have been investigated and several derivatives of it have been prepared.

4. The structure of the aminocoumarin (II = B) has been proved by an independent synthesis starting with *p*-xylohydroquinone.

Minneapolis 14, Minnesota

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ADDITION REACTIONS OF TETRAFLUOROETHYLENE

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The unusual reactivity of the carbon—carbon double bond of tetrafluoroethylene brings about the participation of this versatile fluoroölefin in vinyl polymerization (1), cycloalkylation (2), and addition reactions (3). This paper reports further transformations of tetrafluoroethylene involving the addition of active hydrogen compounds, halogen, and analogous reactants.

An important addition reaction is that of an alcohol with tetrafluoroethylene to obtain the corresponding alkyl ether.

$$CF_2{=}CF_2 + ROH \rightarrow HCF_2CF_2OR$$

A variety of ethers prepared in this way are listed in Table I in the Experimental Section. It is of interest that tetrachloroethylene does not react (3c) under similar conditions but chlorotrifluoroethylene does (3b, c, e).

In some reactions of active hydrogen compounds with tetrafluoroethylene, for example, with amines, derivatives of difluoroacetic acid are obtained rather than the tetrafluoroethane compound. The mechanism of this unexpected transformation was revealed when it was found that reactions with sodium bisulfite gave both types of products, namely, sodium tetrafluoroethanesulfonate and sodium difluoroacetate.

$$CF_2{=}CF_2 + NaHSO_3 \rightarrow HCF_2CF_2SO_3Na + HCF_2COONa$$

The difluoroacetic acid derivative apparently results from the lability of the fluorine atoms which are removed from the α-carbon atom by hydrolysis.

$$HCF_2CF_2SO_3Na + H_2O \rightarrow [HCF_2COSO_3Na + 2HF] \rightarrow HCF_2COONa + SO_2 + 2HF$$

Sodium tetrafluoroethanesulfonate, the free acid, and selected derivatives including various ammonium salts (Table II) are described below.

With amines and tetrafluoroethylene, a similar reaction apparently occurs *via* the intermediate $\alpha,\alpha,\beta,\beta$-tetrafluoroamines (not isolated) (3b) which are hydrolyzed to N-substituted difluoroacetamides.

$$CF_2{=}CF_2 + RNH_2 \rightarrow [HCF_2CF_2NHR] \rightarrow HCF_2CONHR$$

N-Substituted difluoroacetamides from tetrafluoroethylene and a number of amines are described in the Experimental Section (see Table III). With ammonia, the reaction is similar but involves the formation of difluoroacetonitrile which

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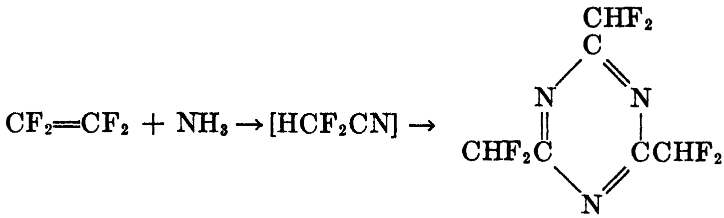
trimerizes immediately so that the product is 2,4,6-tris(difluoromethyl)-*s*-triazine.



The first step is analogous to the reaction of ammonia with asymmetrical dichlorodifluoroethylene to form dichloroacetonitrile, which, however, does not trimerize (10).

An intermediate containing labile fluorine atoms is also formed in the acid-catalyzed reaction of formaldehyde with tetrafluoroethylene. The reaction yields α,α-difluorohydracrylic acid.

$$CF_2{=}CF_2 + CH_2O + H_2O \rightarrow [HOCH_2CF_2CF_2OH] \rightarrow HOCH_2CF_2COOH$$

This reaction is analogous to the synthesis of α,α-dichlorohydracrylic acid from tetrachloroethylene (8).

In addition reactions with halogens and analogous reactants, the tetrafluoroethanes are formed. Thus, iodine yields tetrafluoroethylene diiodide, a dense, distillable liquid. In contrast, iodine does not add to tetrachloroethylene (5). Reaction of tetrafluoroethylene with nitrogen tetroxide gives 1,2-dinitro-1,1,2,2-tetrafluoroethane (13), analogous to the formation of 1,2-dinitro-1,1,2,2-tetrachloroethane from tetrachloroethylene (6).

EXPERIMENTAL

Caution. Information is not available concerning the toxicity of the various fluorine-containing products described. Accordingly, the products should be regarded with suspicion and handled with appropriate care.

1,1,2,2-Tetrafluoroethyl alkyl ethers. The preparation of the tetrafluoroethyl ethers (3a) is illustrated by the etherification of ethanol and of ethylene glycol as described in the following paragraphs. The properties of the various 1,1,2,2-tetrafluoroethyl alkyl ethers prepared from ethanol, *n*-dodecanol, *n*-octadecanol, cyclohexanol, and ethylene glycol are listed in Table I.

1,1,2,2-Tetrafluoroethyl ethyl ether. A stainless steel-lined shaker tube was charged with 90 ml. of absolute ethyl alcohol and 0.5 g. of sodium. The tube was swept with nitrogen, evacuated, and charged with 75 g. of tetrafluoroethylene. The tube was placed in a shaker box and heated at 50° under autogenous pressure for eight hours. At the end of this time, the pressure was released through a carbon dioxide-acetone cooled trap in which 2 ml. of liquid collected. The product from the tube was combined with the contents of the trap, and the tube was washed out with absolute alcohol. The combined material was distilled through a precision column, and the fraction boiling at 54° collected. The fraction weighed 101.7 g. which amounts to a 93% yield based on tetrafluoroethylene. This product appeared to contain a small amount of ethanol. As a final means of purification, the crude ether was washed three times with distilled water. After drying over sodium sulfate, the 1,1,2,2-tetrafluoroethyl ethyl ether was distilled, and found to boil constantly at 57.5° at atmospheric pressure.

1,1,2,2-Tetrafluoroethyl ethers of ethylene glycol. A mixture of 65 g. of ethylene glycol,

50 ml. of anhydrous ether, and 0.5 g. of metallic sodium was heated with 50 g. of tetrafluroethylene in a shaker tube at 75° for eight hours under autogenous pressure. Distillation of the product gave a small foreshot (10 g.) boiling at 37–80°/100 mm. which appeared to contain some of the di-ether. The main product boiled from 86–95°/100 mm., and amounted to 49.7 g. Redistillation gave two fractions, the lower-boiling one being the di-ether and the other the monoether. The *bis(tetrafluoroethyl)ether* of *ethylene glycol* (23.7 g.) boiled constantly at 86°/100 mm. The *tetrafluoroethyl β-hydroxyethyl ether* boiled at 94°/100 mm.

Tetrafluoroethanesulfonic acid (7). *Sodium 1,1,2,2-tetrafluoroethanesulfonate.* A silver-lined, high-pressure shaker tube was charged with 100 g. of sodium sulfite and 200 g. of distilled water, and was evacuated to remove air. A sodium bisulfite solution buffered to *p*H 6–7 with borax or disodium phosphate can also be employed with satisfactory results. The tube was then charged with tetrafluoroethylene so that the pressure was 350 lb./sq. in. when the tube was heated at 120°, and was repressured to 350 lb./sq. in. with tetrafluoroethylene whenever the pressure dropped to about 325 lb./sq. in., due to absorption. The

TABLE I

1,1,2,2-TETRAFLUOROETHYL ALKYL ETHERS

ETHER	YIELD, %	B.P., °C.	n_D^{25}	d_4^{25}	MR$_D$ Calc'd[b]	MR$_D$ Found[c]	ANALYSIS FLUORINE, % Calc'd	ANALYSIS FLUORINE, % Found
$HCF_2CF_2OC_2H_5$	93	57.5	1.294	1.1978	22.3	22.4	52.0	51.97
$HCF_2CF_2OC_{12}H_{25}$	99	105/4 mm	1.3968	0.9831	68.5	69.8	26.5	25.5
$HCF_2CF_2OC_{18}H_{37}$[a]	80	170/6 mm.	1.4144	0.9530	96.2	97.1	20.5	20.7
$HCF_2CF_2OC_6H_{11}$	99	86/100 mm.	1.3848	1.1526	38.6	40.7	38.0	37.3
$(HCF_2CF_2OCH_2—)_2$	9	86/100 mm.	1.3202	1.4726	33.2	35.3	58.0	53.4
$HCF_2CF_2OCH_2CH_2OH$	15	94/100 mm.	1.3418	1.4159	23.8	24.1	46.9	46.3

[a] M.P., 20–23°.

[b] Calculated employing 1.1 as the atomic refraction (AR$_F$) of fluorine.

[c] Based on the formula of Lorenz and Lorentz. See Shriner and Fuson, "The Systematic Identification of Organic Compounds," 3rd Edition, John Wiley and Sons, Inc., New York, N. Y., (1948), p. 45.

reaction proceeded smoothly, and there was a total pressure drop of about 1500 lb. over a period of nine hours at 120°. The reaction mixture was filtered to remove 17 g. of sodium fluoride. The filtrate was evaporated to dryness on a steam-bath, and the solid residue was extracted with hot absolute alcohol. The alcohol extract was evaporated on a steam-bath to obtain a mixture of salts (177 g.), which melted on the Maquenne block at 175°.

1,1,2,2-Tetrafluoroethanesulfonic acid monohydrate. The above reaction product (165 g.) was acidified with 135 ml. of 35% sulfuric acid, and the solution was filtered to remove the precipitated sodium sulfate. The filtrate was extracted several times with ether, the extract was dried, and the ether was removed. The residue was distilled under reduced pressure. After removing the low-boiling material which consisted of water and difluoroacetic acid, the tetrafluoroethanesulfonic acid monohydrate (75 g.) was found to distill at 112–114.5°/5 mm. The acid solidified (m.p. 54°) in the receiver, and was very hygroscopic.

Anal. Calc'd for $C_2H_4F_4O_4S$: F, 38.0; S, 16.0; Neut. equiv., 200.

Found: F, 39.74; S, 16.10; Neut. equiv., 198.8.

1,1,2,2-Tetrafluoroethanesulfonic acid. Tetrafluoroethanesulfonic acid monohydrate (40 g.) was treated with 35 ml. of thionyl chloride in a 125-ml. Claisen flask fitted with a reflux condenser. The compound was not soluble in thionyl chloride, and on warming gently on a steam-bath two layers were formed. After about an hour, the evolution of sulfur dioxide and hydrogen chloride ceased and only one layer remained. The product was distilled under

reduced pressure to obtain a nearly quantitative yield of the anhydrous 1,1,2,2-tetrafluoroethanesulfonic acid boiling at 90–92°/3.5 mm.

Anal. Calc'd for $C_2H_2F_4O_3S$: Neut. equiv., 182. Found: Neut. equiv., 183.

Ammonium salts of 1,1,2,2-tetrafluoroethanesulfonic acid. Reaction of the anhydrous acid with amines, or of the monohydrate with an appropriate isocyanate, gave the corresponding ammonium tetrafluoroethanesulfonates listed in Table II.

The monohydrate or anhydrous tetrafluoroethanesulfonic acid with aniline gave a colorless solid melting at about 235° on the Maquenne block. The salt was soluble in water, ethanol, ethyl acetate, and dioxane but was insoluble in ether and petroleum ether.

TABLE II

SALTS OF 1,1,2,2-TETRAFLUOROETHANESULFONIC ACID WITH AMINES

AMINE	M.P., °C.[a]	EMPIRICAL FORMULA	ANALYSIS				NEUT. EQUIV.	
			N		S			
			Calc'd	Found	Calc'd	Found	Calc'd	Found
Aniline	235	$C_8H_9F_4NO_3S$	—	—	11.64	11.66	275	273.3 274.3
α-Naphthylamine	225	$C_{12}H_{11}F_4NO_3S$	4.31	4.05	9.85	9.18	325	322.5 326.5
Ammonia	198							
Methylamine	119–120.5	$C_3H_7F_4NO_3S$	6.57	6.55				
Dodecylamine	155							

[a] Maquenne block.

TABLE III

PROPERTIES OF N-SUBSTITUTED DIFLUOROACETAMIDES

AMIDE	YIELD, %	B.P., °C/MM.	n_D^{25}	d_4^{25}	ANALYSIS					
					MR_D		N, %		F, %	
					Calc'd[b]	Found	Calc'd	Found	Calc'd	Found
$HCF_2CONHC_6H_5$[a]	71	114/5			—	—	8.32	8.32	22.20	22.75
$HCF_2CON(CH_3)C_6H_5$	51	104/4	1.5036	1.2305	44.0	44.5	7.57	8.23	20.55	20.87
$HCF_2CONHC_4H_9$-*n*	90	113/30	1.4112	1.1029	33.3	34.0	9.26	9.44	25.20	24.49
$HCF_2CON(C_4H_9)_2$-*n*	62	107/10	1.4270	1.0158	52.2	52.2	6.75	6.71	18.30	18.52

[a] M.P., 58°.
[b] See Table I, footnotes [b] and [c].

A similar salt was obtained on treating the acid monohydrate with an excess of phenyl isocyanate.

Reaction of tetrafluorothanesulfonic acid with α-naphthylamine gave a solid, which after recrystallization from water, melted at about 225° on the Maquenne block. An identical product was obtained by reacting tetrafluoroethanesulfonic acid monohydrate with α-naphthyl isocyanate.

1,1,2,2-Tetrafluoroethanesulfonyl chloride. Anhydrous tetrafluoroethanesulfonic acid (81 g.) was added slowly to 100 g. of phosphorus pentachloride. The tetrafluoroethanesulfonyl chloride, b.p. 92–92.5° was separated from the phosphorus oxychloride by fractional distillation.

Anal. Calc'd for $C_3HClF_4O_2S$: F, 37.9; Cl, 17.7.
Found: F, 40.2; Cl, 18.3.

N-Substituted difluoroacetamides. These derivatives were prepared by the reaction of tetrafluoroethylene with aniline, N-methylaniline, *n*-butylamine, and di-*n*-butylamine (9). The properties of the amides are listed in Table III. A typical preparation involving the reaction of tetrafluoroethylene and aniline follows.

Difluoroacetanilide. A stainless steel-lined shaker tube was charged with 93 g. of freshly distilled aniline and 15 g. of borax ($Na_2B_4O_7 \cdot 10H_2O$). The tube was swept with nitrogen, closed, cooled in carbon dioxide–acetone, and charged with 50 g. of tetrafluoroethylene. The mixture was heated with shaking at 130° for eight hours. The product was washed with a saturated solution of potassium carbonate, dried over potassium carbonate, and distilled. The distillate consisted of 51.4 g. of recovered aniline, and 61.6 g. (71% yield) of difluoroacetanilide boiling at 90°/1 mm. and at 114°/5 mm. The difluoroacetanilide melted at 58°. Difluoroacetanilide has been reported (12) as boiling at 259.8° and melting at 52.4°.

Difluoroacetonitrile trimer. When tetrafluoroethylene is allowed to react with ammonia under anhydrous conditions at room temperature, an exothermic reaction occurs with the formation of a bright red product which can be separated into a white solid (ammonium fluoride) and an ether-soluble portion shown to be *2,4,6-tris-(difluoromethyl)-s-triazine.* When the reaction between tetrafluoroethylene and ammonia is not moderated by copper acetate, the reaction may become violently exothermic.

A stainless steel-lined shaker tube was charged with 100 ml. of ether and 0.1 g. of copper acetate. The bomb was blanketed with nitrogen, cooled, evacuated, and charged with 50 g. of anhydrous ammonia and 75 g. of tetrafluoroethylene. The mixture was kept at room temperature for six hours with shaking. The gas was released through a carbon dioxide–acetone cooled trap in which about 30 ml. of bright red liquid collected. The shaker tube contained a bright pink solid weighing about 130 g. The pink solid and red liquid were combined with the bomb washings, and extracted in a Soxhlet apparatus with anhydrous ether. The ether extract was fractionated. The principal product boiled at 75°/10 mm. and corresponded in composition to the trimeric form of difluoroacetonitrile. It amounted to 47.1 g. or an 82% yield. When redistilled, the colorless product boiled at 73°/9 mm., melted at 24.5°, and had the following physical properties: n_D^{25} 1.3999; d_4^{25} 1.5973.

Anal. Calc'd for $(C_2HF_2N)_3$: F, 49.4; N, 18.2; Mol. wt., 231.
Found: F, 47.0; N, 18.09 (K), 17.81 (D); Mol. wt., 213 (ebullioscopic method in benzene).

The trimeric product does not react with bromine in carbon tetrachloride, with dilute aqueous permanganate, or with very dilute nitrous acid.

Hydrolysis of 2,4,6-tris(difluoromethyl)-s-triazine (11). The hydrolysis of 2,4,6-tris(difluoromethyl)-*s*-triazine (22 g.) was carried out by refluxing with 70 ml. of 4 *N* sodium hydroxide for four hours. Ammonia was evolved during the reaction. After separation of unreacted triazine, the aqueous phase was acidified by the addition of 30 ml. of 50% sulfuric acid, and was then extracted with 100 ml. of ether. Fractional distillation of the dried ether extract gave 6 g. of difluoroacetic acid (22% yield) boiling at 131°.

2,4,6-Tris(difluoromethyl)-*s*-triazine (50 g.) was refluxed in water (75 ml.) for fifty hours. The water-insoluble material was separated, washed, dried, and distilled to recover 7 g. of unchanged triazine. Evaporation of the aqueous reaction solution gave 50 g. of salt presumed to be ammonium difluoroacetate. This salt dissolved in hot aqueous sodium hydroxide with the liberation of ammonia. When an aqueous solution of the salt was acidified with conc'd sulfuric acid and extracted with methylene chloride, distillation of the extract gave a liquid identified by boiling point (132°) and neutral equivalent [94] as difluoroacetic acid.

α,α-Difluorohydracrylic acid (14). Paraformaldehyde (15 g.), 150 ml. of conc'd sulfuric acid, and 50 g. of tetrafluoroethylene were heated in a silver-lined shaker tube at 80° for fifteen hours. The product, which evolved fumes of hydrogen fluoride, was poured on 375 g. of ice. After separation of a small amount of oily material and filtration, the mixture was

extracted with four 100-ml. portions of ether, the ether was washed with 50 ml. of water, then extracted with 180 ml. of water containing 20 g. of sodium hydroxide. To the alkaline extract was added with cooling 36 ml. of 50% sulfuric acid. The acidified solution was extracted with four 50-ml. portions of ether. The ether was evaporated, and the syrupy residue was heated under vacuum at 60° for several hours. The weight of the hydgroscopic syrup was 16 g. Fluorine analysis and neutral equivalent indicated that it was 80% α,α-difluorohydracrylic acid. Since the material darkened and increased in viscosity without distilling when heated at 250°/8 mm., it was esterified for purification. The syrup (15 g.), absolute alcohol (23 g.), and 60 g. of anhydrous copper sulfate were heated under reflux on a steam-bath for eleven hours. Distillation of the liquid gave 7.9 g. (n_D^{25} 1.3830) of a pleasant-smelling ester, ethyl α,α-difluorohydracrylate; b.p. 58–61°/6 mm., 181°/760 mm.

Anal. Calc'd for $C_5H_8F_2O_3$: C, 38.97; H, 5.23; F, 24.66.

Found: C, 39.53; H, 5.83; F, 23.1.

The *α,α-difluorohydracrylic acid* obtained upon hydrolysis of the ester melted at 49–53°.

Tetrafluoroethylene diiodide (4). A silver-lined shaker tube was charged with 100 g. of iodine in 150 ml. of ether. The tube was maintained under 300–370 lb./sq. in. of tetrafluoroethylene pressure at 60° for fifteen hours. The product was filtered, washed with sodium thiosulfate solution, then with water, and dried. When distilled it gave tetrafluoroethylene diiodide, b.p. 112–113°, 51°/110 mm., and 23°/14 mm. The product was deeply colored with iodine when distilled at ordinary pressure; when distilled at 14 mm., it had only a faint color. Further discoloration was minimized by storage at temperatures near zero. The yield was 103 g. or 74% based on iodine. It had the following physical properties: n_D^{25} 1.4895; d_4^{25} 2.6293.

Anal. Calc'd for $C_2F_4I_2$: F, 21.48; I, 71.74; MR_D, 37.0.

Found: F, 22.3; I, 68.86; MR_D, 40.3.

1,2-Dinitro-1,1,2,2-tetrafluoroethane. This compound was prepared in glass apparatus at 0° under a few pounds pressure. The apparatus consisted of a 500-ml. filter flask, the side arm of which was connected to an open-end mercury manometer through a T-tube. The remaining end of the T-tube was connected to the tetrafluoroethylene supply through capillary tubing. Connections were made with "Tygon" tubing, since rubber is rapidly attacked by nitrogen tetroxide. A rubber stopper for the flask was coated with sodium silicate, dried, and the lower part covered with aluminum foil. The flask was surrounded with ice and charged with 57 g. of nitrogen tetroxide which had been distilled from phosphorus pentoxide. It is necessary that the nitrogen tetroxide be dry. After flushing the flask with tetrafluoroethylene, the stopper was wired on and the flask was pressured to 7 lb./sq. in. a total of 27 times during three eight-hour periods. Absorption of gas became slow at this point and a permanent pressure developed in the system, caused by the presence of permanent gases from side reactions. The reaction flask was deeply etched. The contents of the flask were poured onto ice, and the liquid (8.8 g.) which separated was washed with water. The yield, based on nitrogen tetroxide, was 7.5%. After drying over magnesium sulfate, the liquid distilled at 58–59°. The colorless 1,2-dinitro-1,1,2,2-tetrafluoroethane so obtained had the following physical properties: n_D^{25} 1.3265; d_4^{25} 1.6024.

Anal. Calc'd for $C_2F_4N_2O_4$: C, 12.51; F, 39.57; MR_D, 22.7.

Found: C, 13.32; F, 38.7; MR_D, 24.2.

The patent literature (13) records the following properties: b.p., 57–58°/750 mm.; sp. gr. (20°) 1.595; n_D^{25} 1.348; MR_D, 25.76.

ACKNOWLEDGMENT

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SUMMARY

A number of new fluorine-containing compounds including several tetrafluoroethyl ethers, tetrafluoroethanesulfonic acid, certain difluoroacetamides, a

tris(difluoromethyl)-s-triazine, difluorohydracrylic acid, and tetrafluoroethylene diiodide have been synthesized by reactions of tetrafluoroethylene with alcohols, sodium bisulfite, amines, ammonia, formaldehyde, and iodine. In reactions with these agents, tetrafluoroethylene is appreciably more reactive than tetrachloroethylene.

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[COMMUNICATION NO. 1245 FROM THE KODAK RESEARCH LABORATORIES]

SOME MACROCYCLIC OXALACTONES AND RELATED SUBSTANCES

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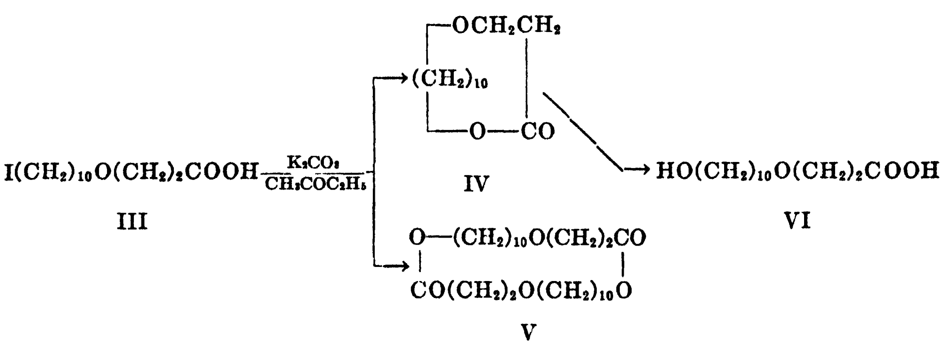
Many macrocyclic ketones and lactones are very useful to the perfumer on account of their musklike odor. The synthesis of even the most accessible is fairly complicated, the lactones, as a rule, being less readily obtainable (1). It is not essential that all ring members of the cyclic ketones be carbon atoms,[1] nor that the heterocyclic lactones have only one oxygen atom in the ring. In this paper there are described the preparations of lactones having several hetero atoms and of a possible intermediate for a heterocyclic ketone.

Decamethylene chlorohydrin (2) adds to acrylonitrile to give 14-chloro-4-oxatridecanonitrile (I), which is easily hydrolyzed to the corresponding acid (II). On treatment with sodium iodide in acetone, the chloro acid is converted to the iodo acid (III). The latter is then cyclized to the 15-membered lactone (IV) of 14-hydroxy-4-oxatetradecanoic acid in a yield of 76%, following Hunsdiecker's procedure (3).

$$Cl(CH_2)_{10}OH + CH_2{=}CHCN \longrightarrow \underset{\text{I}}{Cl(CH_2)_{10}O(CH_2)_2CN} \longrightarrow \underset{\text{II}}{Cl(CH_2)_{10}O(CH_2)_2COOH} \longrightarrow$$



The infrared spectra[2] of lactone IV and Exaltolide (cyclopentadecanolide) are compared in Fig. 1. The close similarity is obvious; the major differences occur in the region of the ether linkages.

A dimeric lactone (V) having thirty ring members was also formed, and isolated, in a yield of 1%. These lactones are isomeric with others described in the

[1] Moncrieff (4) gives an excellent review of the syntheses and properties of ether-lactones. See also Moncrieff, "The Chemical Senses," John Wiley & Sons, Inc., New York, pp. 210–215 (1946).

[2] We are indebted to Mr. William Blum, of Distillation Products, Inc., for these data. The thickness of the layer is 0.005 inch.

literature (5, 6). The new monomeric lactone was hydrolyzed to 14-hydroxy-4-oxatetradecanoic acid (VI); it belongs to a general type included in a patent of Firmenich et Cie (7).

The corresponding properties of the two monomeric lactones are compared in Table I.

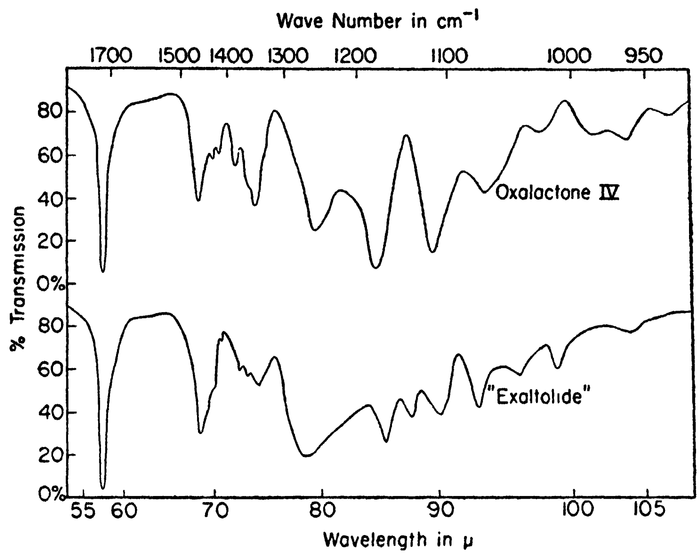


FIG. 1. INFRARED SPECTRA OF OXALACTONE (IV) AND OF EXALTOLIDE

TABLE I

PHYSICAL PROPERTIES OF ISOMERIC OXALACTONES

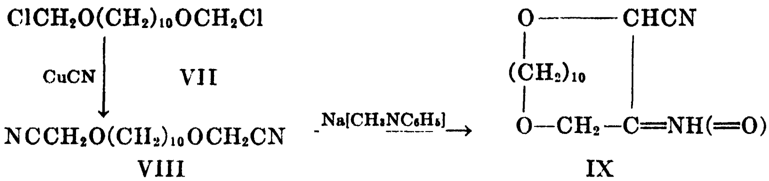
LACTONE FROM	M.P., °C.	B.P., °C.	d_4^{26}	n_D^{26}	MOL. REFR. Obs.	Calc'd	Diff.
14-Hydroxy-4-oxatetra-decanoic acid	1.5	135–137/2 mm.	1.012	1.4670	62.54	63.33	−0.79
14-Hydroxy-12-oxatetra-decanoic acid (6)	8.0	108–111/1 mm.	0.9916[a]	1.4645[a]	63.52	63.39	+0.13

[a] Temp., 33°.

The monomeric oxalactone (IV) has a fine, sweet odor, resembling that of Exaltolide.

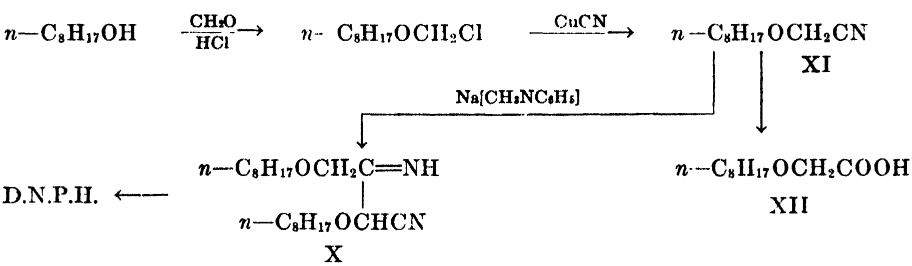
A different approach to the many-membered heterocyclic ketones also starts with decamethylene glycol, which is easily converted to decamethylenedioxymethyl chloride (VII) by means of formaldehyde and hydrogen chloride (8). The chloride reacts with cuprous cyanide (9) to give decamethylene-1,10-dioxymethyl cyanide (VIII). This dinitrile is then cyclized by Ziegler's high-dilution technique (10) to the iminonitrile (IX). The cyclic imine in an acidic

solution gave a 2,4-dinitrophenylhydrazone and a nictazone.[3] It appears that the imino group is hydrolyzed off as anticipated. Attempted hydrolysis of the ketonic nitrile was not successful, complete decomposition taking place; there was no musklike odor at any time. The only recognizable product was decamethylene glycol.



For purposes of comparison, an attempt was made to cyclize 1,16-dicyano-3,14-dioxahexadecane, $NC(CH_2)_2O(CH_2)_{10}O(CH_2)_2CN$ (11, 12), by the same procedure; surprisingly, it resulted mainly in *beta* cleavage, a 90% recovery of decamethylene glycol being obtained.

Because of the unexpected difficulty in the hydrolysis of the imino group of IX, a model compound, 12-cyano-9,13-dioxaheneicosanimide-11 (X) was prepared, as shown below in the outline, with a view to determining the optimum conditions for acid hydrolysis. However, extensive decomposition occurred in all attempts; the only recognizable product was *n*-octyl alcohol. The imine did give a 2,4-dinitrophenylhydrazone, like its cyclic analog.



The octyloxynitrile (XI), on the contrary, was very stable, being readily hydrolyzed to the octyloxyacid (XII) in both alkaline and acid solution.

EXPERIMENTAL

14-Chloro-4-oxatridecanonitrile (I). Acrylonitrile (29 g.) was slowly added to a well-stirred mixture of 96 g. of decamethylene chlorohydrin, 50 ml. of dioxane, and 1 ml. of trimethylbenzylammonium hydroxide, the temperature being kept below 38°. After it had been stirred for two hours at room temperature, the reaction mixture was poured into water, acidified by acetic acid, and extracted with ether. After removal of the solvent from the dried solution, the residual oil was distilled; 17.5 g. of forerun (up to 170°) was followed by the main fraction (82 g., 70%); b.p. 170–174°/5 mm.; n_D^{20} 1.458.

Anal. Calc'd for $C_{13}H_{24}ClNO$: N, 5.7. Found: N, 5.6.

[3] N-Methyl-β-carbohydrazidopyridinium *p*-toluenesulfonate is an excellent reagent for use in the identification of carbonyl compounds (16), but the name is too lengthy for convenience. Dr. F. P. Pingert, formerly of these Laboratories, proposed that the reagent be called "Nictazine," and the derivatives, "Nictazones."

14-Chloro-4-oxatetradecanoic acid (II). A mixture of 40 g. of the chloronitrile, and 100 ml. each of acetic and hydrochloric acids, was refluxed for five hours; the initially clear solution soon became turbid. It was then poured into 250 ml. of water and extracted with two 350-ml. portions of ether. After drying, the solvent was evaporated, leaving 36.5 g. (86%) of crystalline acid; m.p. 33–35°. The analytical sample was recrystallized from petroleum ether; m.p. 36–37°.

Anal. Calc'd for $C_{13}H_{25}ClO_3$: C, 59.0; H, 9.6.

Found: C, 58.9; H, 9.5.

The corresponding amide resulted when the nitrile (2 g.) was dissolved in 10 ml. of conc'd sulfuric acid at −10° and allowed to stand overnight, followed by dilution, filtration, and solution in ethylene chloride. A sodium carbonate wash ensured the absence of traces of acid. The yield was 1.8 g. (84%). The analytical sample was recrystallized from ligroin; m.p. 81–82°.

Anal. Calc'd for $C_{13}H_{26}ClNO_2$: C, 59.4; H, 9.9.

Found: C, 59.5; H, 10.1.

14-Iodo-4-oxatetradecanoic acid (III). A mixture of 36.5 g. of the chloro acid and 23.1 g. of sodium iodide in 300 ml. of acetone was refluxed for 48 hours; 7.1 g. of salt separated. After removal of the solvent, the residue was triturated with 250 ml. of water, the insoluble portion collected on a filter, and then dissolved in ether. On spontaneous evaporation of the dried solution, the iodo acid crystallized in a yield of 33 g. (68%); m.p. 48–50°. Two recrystallizations from petroleum ether raised the melting point to 54°.

Anal Calc'd for $C_{13}H_{25}IO_3$: C, 43.8; H, 7.0.

Found: C, 43.7; H, 7.0.

Lactone (monomeric) of 14-hydroxy-4-oxatetradecanoic acid (IV). The cyclization was accomplished in a high-dilution apparatus, modified as shown in Fig. 2. A, B, and C are female standard-taper 24/40 ground-glass joints; E is a similar male joint. Two dilution wells (D) of about 10-ml. capacity are placed under the joints A and B, above which are attached efficient reflux condensers, protected from moisture, each with a drip tip, so that the condensate drops into the wells. A 300-ml. Hershberg dropping-funnel (14) is attached to C. The reaction flask, attached at E, is of suitable size, and is heated by a Glas-Col mantle. This apparatus is much more compact and less complicated than that previously used for high-dilution reactions.

A typical run was carried out as follows: In the flask were placed 200 g. of potassium carbonate and 3 l. of dry methyl ethyl ketone; the solvent was heated so as to maintain vigorous refluxing in both condensers. A solution of 71 g. of 14-iodo-4-oxatetradecanoic acid in 300 ml. of dry methyl ethyl ketone was added from the Hershberg funnel over a period of 48 hours. The cooled reaction mixture was then filtered, and the solvent evaporated; when the volume had been reduced to about 200 ml., 3.1 g. of white crystals of the dimeric lactone (V) separated, and were collected by filtration. Concentration of the filtrate to about 75 ml., followed by the addition of 50 ml. of petroleum ether gave a little more of the solid. This was removed and the residual oil fractionated *in vacuo*: 1st fraction (5 g.), b.p. up to 75°/2 mm., n_D^{30} 1.4340; 2nd (7 g.), 75–170°/2 mm., n_D^{30} 1.4410; 3rd (36 g.), 130–140°/2 mm., n_D^{30} 1.4650. The last fraction was redistilled; the portion which was collected had b.p. 135–137°/2 mm., n_D^{30} 1.4650 (n_D^{27} 1.4670); freezing point, 1.5°.

Anal. Calc'd for $C_{13}H_{24}O_3$: C, 68.4; H, 10.5; Mol. wt., 228.

Found: C, 68.8; H, 10.4; Mol. wt. (boiling C_6H_6), 224.

Dimeric lactone: 2,17-Diketo-1,5,16,20-tetraoxatriacontane (V). The solid isolated from the solution of the monomer was recrystallized from methanol; m.p. 118–119°.

Anal. Calc'd for $C_{26}H_{48}O_6$: C, 68.4; H, 10.5; Mol. wt., 456.

Found: C, 68.5; H, 10.3; Mol. wt. (in boiling C_6H_6), 464.

14-Hydroxy-4-oxatetradecanoic acid (VI). A mixture of 2 g. of the lactone, 10 ml. of water, and 5 ml. of 5% sodium hydroxide solution was heated on the steam-bath for two hours; the reaction mixture was nearly solid the next day. Water was added (about 60 ml.) to give a clear solution when heated on the steam-bath, Norit added for decolorizing, and, after

filtration, 15 ml. of conc'd hydrochloric acid was added. The precipitated oil soon crystallized; it was recrystallized from toluene; 1.4 g., m.p. 61–62°.

Anal. Calc'd for $C_{13}H_{26}O_4$: C, 63.4; H, 10.6.

Found: C, 63.7; H, 10.8.

The *acid hydrazide*, m.p. 116–117°, was obtained in the usual way from the monomeric lactone and 85% hydrazine hydrate. It crystallizes well from alcohol or ligroin.

Anal. Calc'd for $C_{12}H_{26}N_2O_3$: C, 58.5; H, 10.6.

Found: C, 58.8; H, 10.5.

1,16-Dicyano-3,14-dioxahexadecane was found to crystallize from ligroin (b.p. 90–120°), whereas in the literature (11, 12) it is described as an oil. It melts at 44–45°.

Anal. Calc'd for $C_{16}H_{28}N_2O_2$: N, 10.0. Found: N, 9.9.

1,14-Dichloro-2,13-dioxatetradecane, decamethylenedioxymethyl chloride (VII). A mixture of 100 g. of decamethylene glycol, 35 g. of paraformaldehyde ("trioxymethylene"), and 1

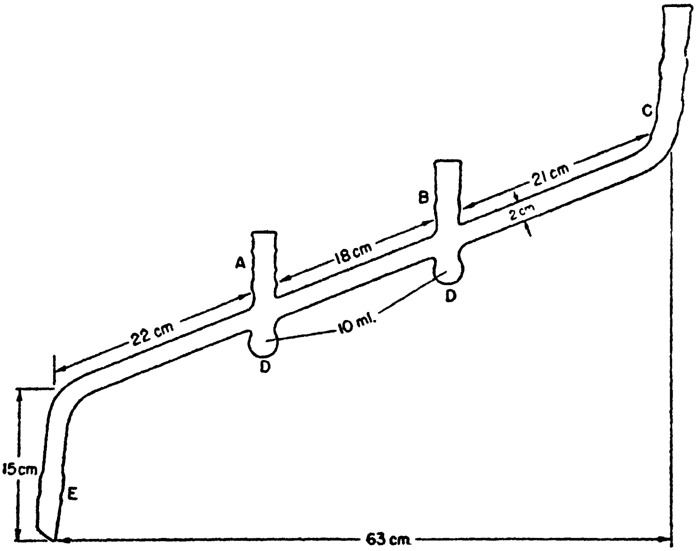


FIG. 2. HIGH-DILUTION MIXER

l. of benzene was saturated with hydrogen chloride at 5–10°; all the solid had gone into solution after four hours (8). The benzene layer was separated and distilled. The chloride boils at 200–203°/15 mm.

Anal. Calc'd for $C_{12}H_{24}Cl_2O_2$: Cl, 26.3. Found: Cl, 26.0.

1,14-Dicyano-2,13-dioxatetradecane (VIII). To a rapidly-stirred suspension of 50 g. of cuprous cyanide in 114 ml. of toluene, 67.5 g. of the chloride (VII) was slowly added. The brown solution was refluxed nine hours more, filtered, and distilled. The yield of nitrile, b.p. 219–220°/4 mm., was 87% (9, 15). It solidified on chilling, and was recrystallized from alcohol (4 ml. per g.); m.p. 33–34°.

Anal. Calc'd for $C_{14}H_{24}N_2O_2$: N, 11.1. Found: N, 10.8.

1-Cyano-4,15-dioxacyclopentadecanimide-2 (IX). The catalyst was prepared as directed in the literature (13), using 3 l. of dry ether, in dry nitrogen. When the vigorous reaction had subsided, 50.4 g. of decamethylenedioxymethyl cyanide in 500 ml. of dry ether was added over a 3-day period, using Ziegler's apparatus (10). One liter of water was added slowly, the layers separated, the ether layer was washed with dilute hydrochloric acid (170 ml. of conc'd acid diluted to 1500 ml.) to remove the methylaniline, and decanted

from a little solid. After drying and fractional distillation, 19 g. of the cyclic imide, b.p. 155–167°/1 mm., was obtained (9, 15). It was recrystallized from 50 ml. of ligroin, 18 g. being recovered. The analytical sample melted at 75–76°.

Anal. Calc'd for $C_{14}H_{24}N_2O_2$: N, 11.1; Mol. wt., 252.

Found: N, 11.1; Mol. wt. (in boiling C_6H_6), 246, 247.

Hydrolysis. A 3.4-ml. portion of conc'd sulfuric acid was diluted to 62 ml., and 15 ml. of chloroform and 2.4 g. of the cyclic imine were added; the mixture was then refluxed for two hours, the chloroform layer separated and the solvent evaporated. The residue was used directly. One portion was refluxed with methanolic potassium hydroxide, diluted, and the solid collected; it melted at 70–71° after recrystallization from ethyl acetate, and was identified as decamethylene glycol by a mixed melting point. This glycol also resulted by five hours' refluxing of the imine with hydrochloric acid.

2,4-Dinitrophenylhydrazone. This derivative was prepared from a portion of the chloroform residue above; bright yellow crystals were formed; m.p. 114–115°.

Anal. Calc'd for $C_{20}H_{27}N_5O_6$: N, 16.1. Found: N, 16.2.

Nictazone. Another portion of the chloroform residue was taken up in methanol and refluxed with Nictazine (16) for two hours. The derivative was isolated from the chilled solution and recrystallized three times from *n*-butyl alcohol; it gave yellow crystals; m.p. 242–243°.

Anal. Calc'd for $C_{28}H_{38}N_4O_6S$: C, 60.2; H, 6.8.

Found: C, 59.9; H, 6.6.

n-Octyloxymethyl cyanide; 1-cyano-2-oxadecane (XI).[4] The crude *n*-octyloxymethyl chloride, prepared in the usual way (8) from 140 g. of *n*-octyl alcohol, 1 l. of benzene, and 30 g. of paraformaldehyde, with saturation by hydrogen chloride, and separation of the benzene layer, followed by removal of the solvent, was taken up in 250 ml. of toluene. After the addition of 90 g. of cuprous cyanide, refluxing for twelve hours, filtering, and distilling, the nitrile (90 g.) was collected at 83–87°/2 mm.

Anal. Calc'd for $C_{10}H_{19}NO$: N, 8.3. Found: N, 8.1.

n-Octyloxyacetic acid (XII) was obtained by alkaline hydrolysis of the nitrile. A mixture of 25 g. of nitrile, 60 ml. of 40% aqueous sodium hydroxide, and 50 ml. of alcohol was heated on the steam-bath for fifteen hours. The alcohol was then evaporated and the residue taken up in 70 ml. of water, the solution filtered, and acidified. The acid was extracted with ether; 22 g. (79%) of crude acid remained after evaporation of the solvent. When dissolved in ligroin and chilled, the acid crystallized; it melted at about 15°. The same acid was also prepared by hydrolysis using 70% sulfuric acid for five hours.

Anal. Calc'd for $C_{10}H_{20}O_3$: C, 63.8; H, 10.6.

Found: C, 63.9; H, 10.8.

12-Cyano-9,13-dioxaheneicosanimide-11 (X)[4] was prepared essentially as described above under the cyclic imide (IX), in a yield of 88%; b.p. 206–210°/2 mm.

Anal. Calc'd for $C_{20}H_{38}N_2O_2$: N, 8.3. Found: N, 8.2.

The *2,4-dinitrophenylhydrazone*, likewise obtained as above, separated from alcohol in bright yellow plates; m.p. 43–45°.

Anal. Calc'd for $C_{26}H_{41}N_5O_6$: N, 13.5. Found: N, 13.6.

SUMMARY

Two macrocyclic oxalactones have been prepared by ring closure of suitably constituted open-chain compounds. The monomeric lactone, which has a musk-like odor, closely resembles a known isomer.

A macrocyclic dioxaimidonitrile has also been prepared. Suitable conditions for hydrolyzing the nitrogenous groups without decomposition were not found.

[4] We wish to thank Dr. Alan Bell, formerly of these Laboratories, for this preparation.

An open-chain dioxaimidonitrile was likewise degraded on hydrolysis, as was a dioxadinitrile.

Rochester 4, New York

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[CONTRIBUTION FROM STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

THE MECHANISM OF THE REACTIONS OF HYDROCARBONS WITH SULFUR[1]

A. WESLEY HORTON[2]

Received February 21, 1949

The reactions of olefins and polyolefins with sulfur at 140° have been discussed recently by Farmer and Shipley (1, 2). These investigators suggested that the sulfur was acting by a free radical mechanism involving either the unsaturation electrons of the hydrocarbons or the active methylene groups.

The main aim of the present research, initiated in September, 1946, has been the elucidation of the mechanism of the high temperature (above 200°) reactions of sulfur with hydrocarbons. In gaining an understanding of the fundamental nature of these processes, a study of the products from alkyl-substituted aromatic compounds has proven of considerable value.

In particular, attention has been centered on the hydrocarbons and heterocyclic compounds formed by the reaction of toluene and sulfur. The reported products (3, 4, 5) whose formation has been confirmed by the writer in an unpublished research are bibenzyl, stilbene, tetraphenylthiophene and a previously uncharacterized compound, $C_{14}H_{10}S$. The following products have also been isolated by the earlier investigators: *o*-bitolyl (5), 1,2,3,4-tetraphenylbutane (6), and a substance, $C_{14}H_{10}S_2$ (3). Renard also reported phenylthiophene ($C_{10}H_8S$) among the products. However, although the reactions of his compound were certainly characteristic of a thiophene derivative, the physical properties differed greatly from those reported for either 2- or 3-phenylthiophene (7, 8). Now, in reviewing the early literature on sulfur heterocyclics, the writer has noted a striking agreement between the melting and boiling points of Renard's "phenylthiophene" and those reported for the so-called "tolallyl sulfide", $C_{14}H_{10}S$ (9, 10). This crystalline material had been previously synthesized by the pyrolysis of benzyl sulfide and disulfide. There seems little doubt now, in the light of the writer's own findings, that Renard did isolate some impure "tolallyl sulfide" from the reaction products from toluene and sulfur.

The attempts of the early workers to determine the structure of this compound were unsuccessful. Actually, since 1903 no mention of it has appeared in the literature. In that year, Fromm and Achert (11) reported a vain attempt to repeat Forst's synthesis of "tolallyl sulfide". They came to the unfortunate conclusion that the material previously isolated was nothing more than a mixture of two other products of the reaction and hence suggested that its name be stricken from the record.

[1] Taken from the dissertation presented by the author to the faculty of the Graduate School of Yale University in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1948.

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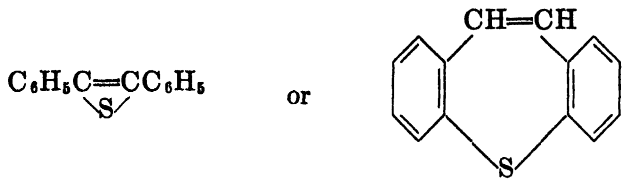
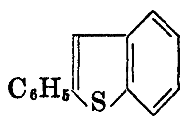
It was obviously essential to any consideration of the mechanism of the reaction to characterize the $C_{14}H_{10}S$ material. The following structures had been suggested by Forst (9):



However, on the basis of the thiophene-like reactions of the compound reported by Renard (3), the following structure seemed more probable to the writer:



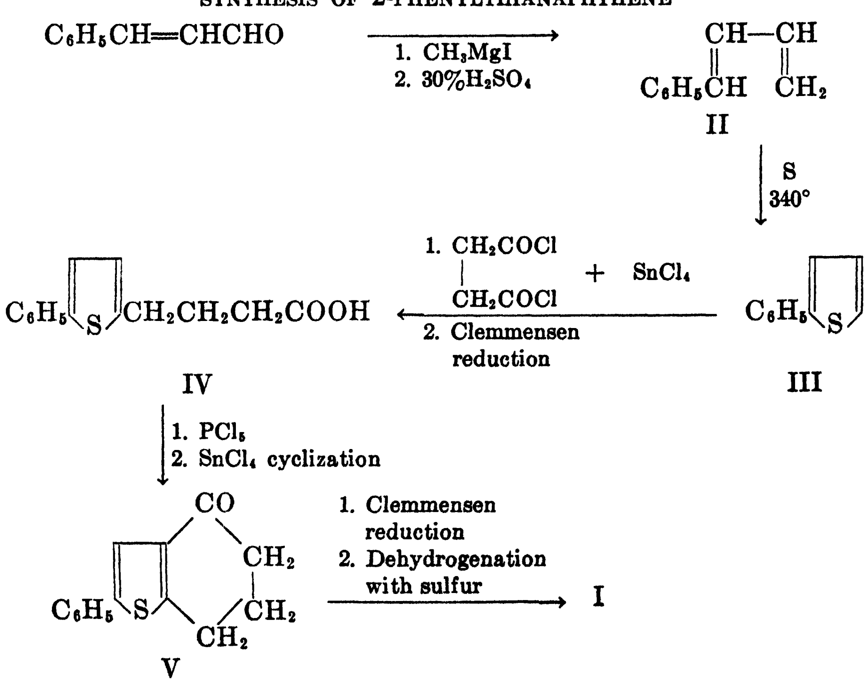
2-phenylthianaphthene

$C_{14}H_{10}S$

I

Since this heterocycle had not been described in the literature as such, its synthesis by standard procedures was undertaken. The following route was employed, the product proving to be identical with the $C_{14}H_{10}S$ product of the reaction of toluene with sulfur:

SYNTHESIS OF 2-PHENYLTHIANAPHTHENE



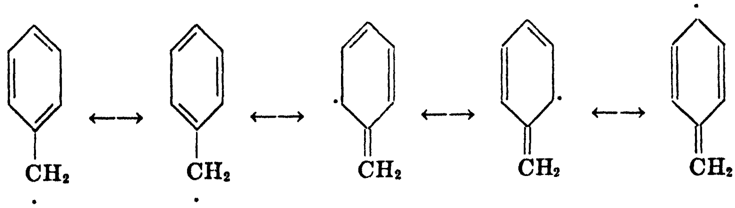
Having established the molecular structures of the main products formed in the reaction of toluene with sulfur, attention may now be directed to the mechanism involved. In this respect, it has proven particularly illuminating to consider possible relationships between various reactions which form directly one or both of the two heterocyclics, 2-phenylthianaphthene, I, and tetraphenylthiophene, VI.

(a) $C_6H_5CH_3 + S$	$\xrightarrow{250°}$	I + VI	
(b) $(C_6H_5CH_2)_2S$	$\xrightarrow{200°}$	I + VI	(9, 10)
(c) $(C_6H_5CH_2)_2S_2$	$\xrightarrow{200°}$	I + VI	(9, 10)
(d) $(C_6H_5CH_2COO)_2Ba$	$\xrightarrow{S}$	I + VI	(12)
(e) $(C_6H_5CHS)_x$	$\xrightarrow{\Delta}$	only VI	(10, 13)
(f) $C_6H_5CH_2OH + S$	$\xrightarrow{200°}$	C_6H_5CHO + VI	(14)
(g) $C_6H_5CH_2CH_2C_6H_5$	$\xrightarrow{\text{S at } 230°}$	I + VI	(6, 14)
(h) $C_6H_5CH{=}CHC_6H_5$	$\xrightarrow{\text{S at } 230°}$	only VI	(6,10)

It is to be noted especially that the thianaphthene derivative, I, was formed only in the reactions of those starting materials which contained the $C_6H_5CH_2$ grouping. Reaction (f) of benzyl alcohol is not necessarily an exception to this rule since its conversion by sulfur probably proceeds by the following steps:

$$C_6H_5CH_2OH + S \rightarrow C_6H_5CHO + H_2S$$
$$C_6H_5CHO + H_2S \rightarrow C_6H_5CHS + H_2O$$
$$C_6H_5CHS \rightarrow \text{VI [see reaction (e)]}$$

The fact that compound I is not formed by reaction (h), even though stilbene has the same carbon structure as I, is strong indication that the benzyl (or 1,2-diphenylethyl) radical is essential for the cyclization to a thianaphthene structure. Since the benzyl radical exists as a resonance hybrid with important contributions from the following structures, the path that is open for the coupling of sulfur in the *ortho* position is quite evident.



The free radical nature of pyrolytic reactions such as (b) and (c) has long been recognized. Physical evidence to support this hypothesis was recently obtained by Cutforth and Selwood (15), who demonstrated by magnetic measurements

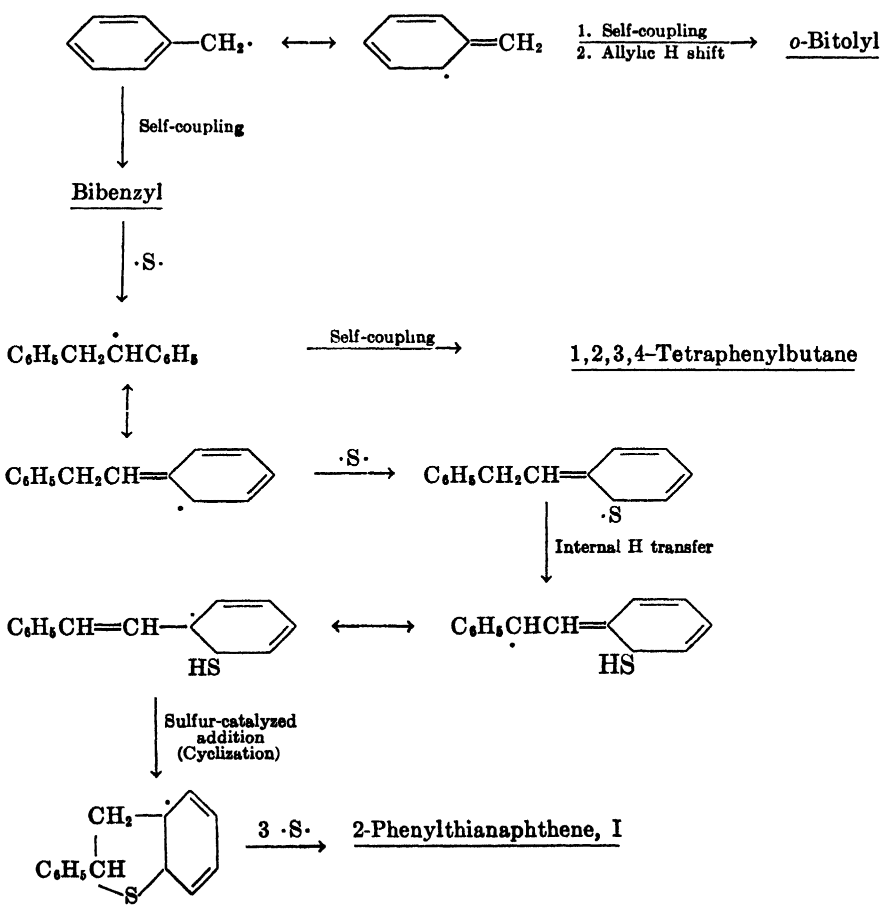
that aryl disulfides form free radicals in large amounts by thermal dissociation. Furthermore, it seems quite probable that reaction (d) is closely analogous to the Kolbe electrolytic synthesis of hydrocarbons, a classical example of a coupling best explained by a free radical mechanism (16).

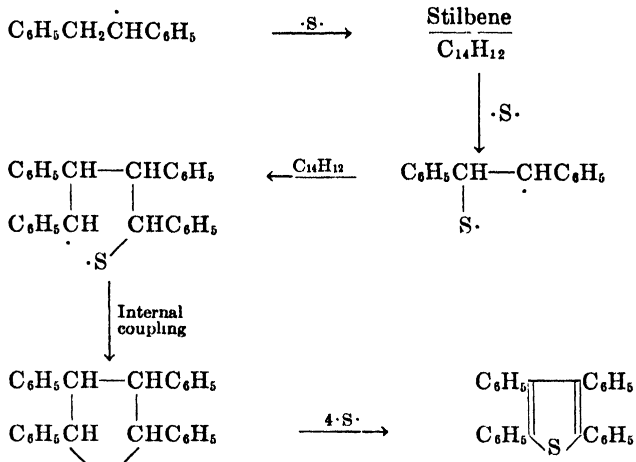
Thus, it is seen that the data not only strongly indicate but seem almost to demand a free radical mechanism for the attack of sulfur on the side chains of aromatic hydrocarbons such as toluene. Utilization of such a theory permits a ready explanation of the formation of all reported products. The sulfur atom or a molecular chain, $\cdot(S_n)\cdot$, where n = 2 to 8, is believed to act as a radical in the various dehydrogenation steps. For example,

$$C_6H_5CH_3 + \cdot S\cdot \rightarrow C_6H_5CH_2\cdot + H:S\cdot$$

The HS· radicals formed are, of course, equally effective as hydrogen acceptors in subsequent reaction steps.

The following series of reactions is presented to illustrate the usefulness of the general concept. Products isolated are underlined.



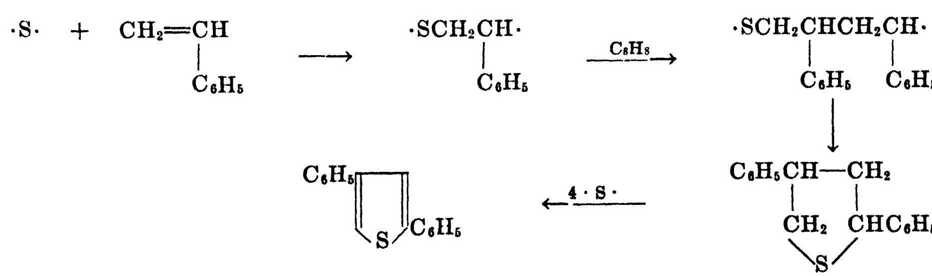


VI

It is evident that it is possible to write several other sequences of such free-radical reactions to explain the formation of the two heterocyclic compounds.

The application of the free radical theory to the mechanism of the reaction of ethylbenzene with sulfur (17) has some interesting aspects. No thianaphthene was obtained by Glass and Reid from the product mixture, 2,4-diphenylthiophene, VII, being the only sulfur-containing organic compound isolated. The same heterocycle and a very small amount of the 2,5-substituted isomer were obtained by Baumann and Fromm (13) by the reaction of styrene with sulfur. The obvious assumption is made that the olefin is the intermediate in the conversion of ethylbenzene to the thiophene derivatives. The phenylethyl radical formed in the initial step would be expected to disproportionate very readily to styrene.

It is now postulated that the further reaction of styrene with sulfur (like that of stilbene and sulfur) proceeds by a mechanism exactly like that generally accepted for the free radical-catalyzed polymerization of such unsaturates (18).

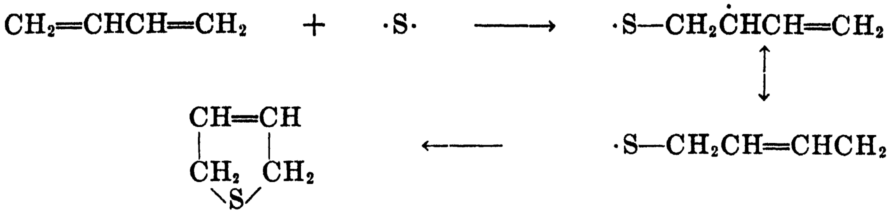


VII

Since the initiating sulfur radical bears two unpaired electrons, the chain reaction is terminated by cyclization as soon as the necessary spatial configuration for stable ring formation obtains. Furthermore, since styrene polymerization proceeds almost exclusively by the "head-to-tail" mechanism pictured, very little

2,5- or 3,4-diphenylthiophene should be formed. This is in accord with the reported results.

The cyclization of conjugated dienes with sulfur (19) probably involves a similar mechanism. The following sequence is suggested:

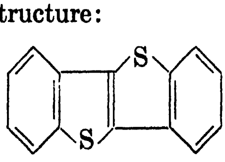


An alternative explanation which does not differ basically from that above involves the picture of the butadiene molecule described by Pauling (20), who gave evidence that structure B below makes an important contribution (20%) to the resonance hybrid:

$$\underset{\text{A}}{CH_2{=}CH{-}CH{=}CH_2} \longleftrightarrow \underset{\text{B}}{\cdot CH_2{-}CH{=}CH{-}CH_2\cdot}$$

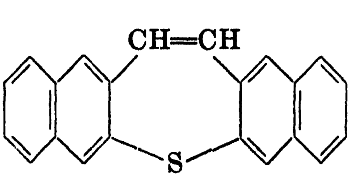
The cyclization with sulfur would then proceed by a 1:4 coupling with structure B, yielding again 2,5-dihydrothiophene, which may be readily dehydrogenated to the fully aromatic heterocycle. The formation of the by-product, thiophene thiol, in the commercial synthesis of thiophene may be nicely explained as a sulfur-catalyzed addition of hydrogen sulfide (21, 22) to this intermediate cyclic olefin, followed by the usual dehydrogenation.

The general mechanism herein developed has been of value not only in explaining the formation of all known products of the reactions of hydrocarbons with sulfur, but also in predicting the molecular structures of several heterocyclic compounds with have been isolated but not characterized. Thus, the $C_{14}H_{10}S_2$ compound isolated by Renard (3) from the products from toluene and sulfur probably has the following structure:

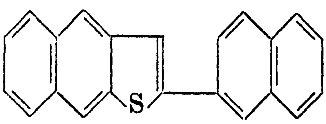


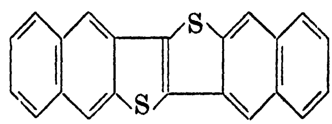
$C_{14}H_8S_2$

From the reaction of β-methylnaphthalene with sulfur, Friedmann (5) isolated products with the empirical formulas, $C_{22}H_{14}S$ and $C_{22}H_{14}S_2$. For the former he suggested the following structure:

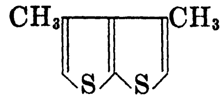


However, it seems to the writer that the five-membered heterocyclic ring system was probably formed as follows:

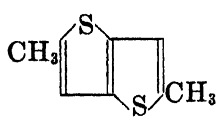

$C_{22}H_{14}S$


$C_{22}H_{12}S_2$

Friedmann (5) also reported on the reactions of aliphatic hydrocarbons with sulfur under pressure. From *n*-octane he produced a thiophthene derivative to which he assigned the following structure:


$C_8H_8S_2$

Since the formation of this compound would involve a highly improbable isomerization of the hydrocarbon skeleton, it seems much more likely that the product obtained by Friedmann had the structure:



EXPERIMENTAL[3]

1-Phenyl-1,3-butadiene, II. This diolefin was obtained in 69% yield from the reaction of cinnamaldehyde and methyl magnesium iodide by a modification of the method described by Heide (23).

2-Phenylthiophene, III. To a 1-l. flask equipped with a dropping-funnel and a downward condenser for vacuum distillation was added 310 g. (9.7 g. atoms) of sulfur. This was melted and heated to 340°. The pressure was reduced to about 300 mm. and then, while the sulfur was stirred magnetically, 99 g. (0.62 mole) of 1-phenylbutadiene was added dropwise in 30 min. The yellow distillate which formed during the addition was diluted with acetone and filtered to free it from some unreacted sulfur. The solvent was evaporated and the residue fractionated *in vacuo* through a 2-foot Widmer column. Four and five-tenths grams of unreacted diene was recovered as a forerun, followed by 23 g. of phenylthiophene, boiling at 93–95°/3 mm. The product crystallized on cooling, m.p. 34–35°.

Yields obtained by this method were comparable to those from the reaction of sodium β-benzoylpropionate with phosphorus trisulfide (24).

The *mercuriacetate derivative* of the 2-phenylthiophene was prepared in small quantity and recrystallized from absolute alcohol, m.p. 174–175°.

Succinylation of thiophene. This reaction had been successfully accomplished by the use of succinic anhydride and aluminum chloride (25). In the present study, it was found that neither stannic chloride nor iodine would catalyze the substitution However, β-thenoylpropionic acid was obtained in good yield by the reaction of thiophene with succinyl chloride and stannic chloride in benzene at −5°.

γ-(5-Phenyl-2-thienyl)butyric acid, IV. To a stirred solution of 2 g. (0.0125 mole) of 2-phen-

[3] All temperatures reported were corrected against NBS–calibrated thermometers.

ylthiophene and 2.0 g. (0.0129 mole) of succinyl chloride in 6 cc. of benzene, held at −10°, was added dropwise a solution of 6 g. (0.0228 mole) of stannic chloride in 8 cc. of benzene. Twenty minutes were required for the addition and the mixture was stirred ten minutes longer as it was allowed to warm to 0°.

The reaction product was hydrolyzed with 5 cc. of ice-water. The benzene solvent and some unreacted phenylthiophene were steam-distilled.

The residue was washed with copious quantities of water and then dissolved in 20 cc. of 5% aqueous sodium carbonate. The alkaline solution was washed twice with ether. Acidification with conc'd hydrochloric acid precipitated the keto acid as a pink solid, weighing 1.5 g. (Yield, 46%). Recrystallization from acetone (decolorization with Norit) gave an almost colorless crystalline product, m.p. 204–205°.

Anal. Calc'd for $C_{14}H_{12}O_3S$: S, 12.3. Found: S, 12.6.

Neut. equiv. Calc'd: 260. Found: 260.

The keto acid was reduced to the butyric acid derivative, IV, by the Clemmensen method. Fifteen grams of mossy zinc was amalgamated by shaking for five minutes with a solution of 1.5 g. of mercuric chloride and 1.5 cc. of conc'd hydrochloric acid in 23 cc. of water. The aqueous solution was then decanted and the zinc amalgam covered with 45 cc. of glacial acetic acid, 27 cc. of conc'd hydrochloric acid and 3.50 g. (0.0135 mole) of β-(5-phenyl-2-thenoyl)propionic acid. The mixture was allowed to stand for 65 hours with occasional shaking and warming, during which time an additional 25 cc. of conc'd hydrochloric acid was added in small portions. Finally, 15 cc. of toluene was added and the mixture was shaken and refluxed for 30 min. After cooling, the layers were separated. The aqueous layer was extracted twice with toluene. The combined toluene solutions were filtered to remove a suspended solid (0.55 g. of unreacted keto acid). The solvent was then evaporated and the residue dissolved in dil. sodium hydroxide. After filtration, the solution was acidified, the desired acid, IV, precipitating; weight 2.75 g. (yield, 84%). After recrystallization from 95% ethanol, it melted at 100–102°.

Anal. Calc'd for $C_{14}H_{14}O_2S$: S, 13.0. Found: S, 13.1.

Neut. equiv. Calc'd: 246. Found: 248.

2-Phenyl-4,5,6,7-tetrahydrothianaphthen-4-one, V. To a solution of 1.0 g. (0.0041 mole) of the acid, IV, in 5 cc. of dry benzene in a 50-cc. Erlenmeyer flask was added 1.0 g. (0.0048 mole) of powdered phosphorus pentachloride, with swirling and external cooling. After standing at room temperature for an hour, the mixture was warmed on the steam-bath for five minutes, and then chilled until the benzene began to solidify. A cooled solution of 1.0 cc. (0.0086 mole) of anhydrous stannic chloride in 1 cc. of benzene was added rapidly with swirling. After standing for fifteen minutes in ice-water, the mixture was hydrolyzed with ice, followed by 5 cc. of conc'd hydrochloric acid. One-half cubic centimeter of ether was added to hasten the hydrolysis and the mixture was shaken until all the solid tin complex was dissolved. The organic layer was separated, washed with several portions of 5% hydrochloric acid, water, 5% sodium hydroxide, and finally again with water. After drying over sodium sulfate, the solvent was evaporated and the residue sublimed *in vacuo* at a bath temperature of 80–90°/0.01 mm. The sublimate was then recrystallized from methanol. The desired cyclic ketone, V, thus obtained weighed 0.64 g. (yield, 69%); m.p. 108.5–109°.

Anal. Calc'd for $C_{14}H_{12}OS$: S, 14.0. Found: S, 14.2.

2-Phenyl-4,5,6,7-tetrahydrothianaphthene. A mixture of 12 g. of mossy zinc, 1.5 g. of mercuric chloride, 1.5 cc. of conc'd hydrochloric acid, and 23 cc. of water was shaken for 5 minutes. The aqueous solution was decanted and the zinc amalgam washed with water. It was then covered with 30 cc. of acetic acid and 18 cc. of conc'd hydrochloric acid. The ketone, V, 1.20 g. (0.0053 mole), was added and the mixture allowed to stand for 15 hours with occasional shaking and warming to 50°. To complete the reaction, 8 cc. of toluene was then added and the mixture warmed in a water-bath at 80° for 8 hours. After standing overnight, the layers were separated. The toluene solution was washed with dil. sodium bicarbonate and with water, and then dried over sodium sulfate. After evaporation of the solvent, the product was obtained as a yellow solid, weight 1.07 g. Sublimation at a bath

temperature of 60°/0.01 mm., followed by recrystallization from acetone, yielded almost colorless 2-phenyl-4,5,6,7-tetrahydrothianaphthene, melting at 82.5–83.5°.

Anal. Calc'd for $C_{14}H_{14}S$: C, 78.5; H, 6.5.

Found: C, 78.4; H, 7.1.

2-Phenylthianaphthene, I. An intimate mixture of 2.70 g. (0.0126 mole) of the heterocyclic compound described in the previous paragraph, and 0.89 g. (0.0278 g. atom) of sulfur was heated at 235–245° until evolution of hydrogen sulfide ceased (fifteen minutes required). The product was dissolved in 30 cc. of boiling benzene. The solution was cooled and filtered from some unreacted sulfur which crystallized. It was then shaken with two 40-cc. portions of 10% aqueous sodium sulfite to complete removal of elemental sulfur. The solvent was then evaporated and the solid residue sublimed *in vacuo* at a bath temperature of 125–130°/0.1 mm. The colorless sublimate, 2-phenylthianaphthene, weighed 1.12 g. (yield, 42%). After recrystallization from ethanol, the product melted at 175.5–176.0°.

Anal. Calc'd for $C_{14}H_{10}S$: C, 80.00; H, 4.76; S, 15.24.

Found: C, 80.25; H, 4.40; S, 15.47

Forst (9) reported a melting point of 172–173° for his "tolallyl sulfide" obtained by pyrolysis of benzyl sulfide. The $C_{14}H_{10}S$ compound obtained by the writer from the reaction of toluene with sulfur was purified in the same manner as described above for 2-phenylthianaphthene. It then melted at the same temperature (176°) and a mixture with the product synthesized from 2-phenylthiophene showed no depression of the melting point. Identical blue-green dyes were obtained by the reaction of either material with isatin in conc'd sulfuric acid.

Reaction of bibenzyl with sulfur. It had been reported by Szperl (6) that tetraphenylthiophene was the exclusive product of this reaction. Since the general mechanism of the reaction of sulfur with hydrocarbons developed herein seemed to indicate that 2-phenylthianaphthene should also be formed in this reaction, the following experiment was carried out.

Bibenzyl, 50 g. (0.275 mole), was mixed intimately with 26.4 g. (0.825 mole) sulfur and heated at 260–285° for 5 hours. The product was subjected directly to vacuum distillation. A single cut was taken; boiling range 220–250°/22 mm., weight 10 g. The residue (45 g., probably mostly tetraphenylthiophene) was not investigated further. A small part of the distillate was dissolved in benzene, washed with two 50-cc. portions of 10% aqueous sodium sulfite and with water. The solution was dried over calcium chloride and then the solvent evaporated until crystallization began. The solid was redissolved by warming. It recrystallized on cooling and was filtered and dried, m.p. 173–174.5°. A mixture with pure tetraphenylthiophene had m.p. 145–150°. A mixture with 2-phenylthianaphthene, however, had m.p. 173–175°.

Thus, as would be predicted by the free radical mechanism, both heterocyclic compounds are formed by the reaction of bibenzyl with sulfur.

ACKNOWLEDGMENTS

The author is indebted to Professors Werner Bergmann and James English, Jr. for their generous contributions in time and thought to this research problem. He owes much also to the inspiration and guidance of Professor Werner E. Bachmann during his initiation to chemical research some years back.

SUMMARY

A general free radical mechanism of the reactions of hydrocarbons with sulfur has been developed. It has been applied successfully to the explanation of the formation of all known products of the reactions, as well as to the prediction of molecular structures of several heterocyclic compounds which have been isolated but not characterized.

In particular, it was shown that an important product of the reaction of toluene and sulfur was identical with 2-phenylthianaphthene, synthesized by a standard method of ring addition from 2-phenylthiophene. The thianaphthene derivative was, in all probability, the same as a $C_{14}H_{10}S$ product of the pyrolysis of benzyl sulfide, known as "tolallyl sulfide," described in the German literature of 1875–1900.

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[Contribution from The Wellcome Research Laboratories]

UNSYMMETRICALLY DISUBSTITUTED PIPERAZINES. II. HISTAMINE ANTAGONISTS[1]

LEWIS P. ALBRO[2], RICHARD BALTZLY, and ARTHUR P. PHILLIPS

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When tested by the tracheal chain method (1, 2) the known benzylmethyl and benzylethyl piperazines (3) were found to have about 1% and 0.4% respectively of the antihistaminic activity of dimethylaminoethyl benzhydryl ether (Benadryl). This suggested that N-methylpiperazines having N′-substituents containing two or three rings might show activities comparable to those of currently available histamine antagonists and that among such substituents the benzhydryl group would be close to the optimal size.

A variety of derivatives of methylpiperazine, whose properties are shown in Table I, were therefore prepared to ascertain (a) whether the benzhydryl radical was in fact of the optimal size and (b) whether it would be possible to combine the features of antihistaminic and bronchodilator drugs. This latter point early received a negative answer which was not unexpected since attempts to combine in one compound the virtues of two physiologically active types usually result in a substance lacking the advantages of either. Compound XI was much less potent than benzhydrylmethylpiperazine and Compounds XII and XIII had only vestigial activity. Bronchodilator action was also negligible.

In respect to point (a), Compounds I–VI had activities intermediate between those of benzylmethylpiperazine and benzhydrylmethylpiperazine (4). Compounds VII–X and XIV–XV again showed little or no activity. It is evident that the benzhydryl group is, at any rate, close to the optimal size. The inferior potency of Compounds XI–XIII can be interpreted as meaning that hydrophilic groups in this portion of the molecule are undesirable.

EXPERIMENTAL

With the exception of Compounds III and XII, all the substances listed in Table I were prepared by the direct reaction of methylpiperazine with the appropriate halide. The intermediates for I, II, and XIII were bromides, the rest chlorides. The reactions leading to Compounds IV–VI and XIV–XV were carried out in ethanol, the others without solvent except that a little benzene was usually added to ensure adequate mixing. The benzhydryl chloride precursors to Compounds VII–X react by the SN_1 scheme requiring absence of hydroxylic solvents. It is probable from the poor yield of Compound V that α-naphthylmethyl chloride also reacts largely by the "unimolecular" mechanism. In the preparation of Compounds XI and XIII hydroxylic solvents presumably would not be objectionable. Aside from these variations the preparations were of standard type and can be generalized. Two equivalents of methylpiperazine were employed to one of halide and the mixture was heated on the steam-bath for two to ten hours dependent on the expected reactivity of the halide. When ethanol was present it was evaporated at this point. The reaction mixture was then partitioned between ether and water, the ethereal layer being washed with water

[1] The work here reported is part of a joint program carried out in collaboration with a pharmacological group in these laboratories.

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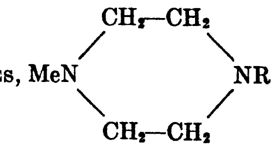
TABLE I

SALTS OF UNSYMMETRICALLY DISUBSTITUTED PIPERAZINES, 

COMP. NO.	R	M.P., °C.[a]	YIELD, %	EMPIRICAL FORMULA	ANALYSES Carbon Calc'd	Carbon Found	Hydrogen Calc'd	Hydrogen Found
I	2-Nitrophenyl	234–235[b]	60	$C_{11}H_{15}N_3O_2 \cdot HCl$	51.24	50.94	6.25	6.13
II	4-Nitrophenyl	269–270[b]	90	$C_{11}H_{15}N_3O_2 \cdot HCl$	51.24	51.46	6.25	6.06
III	4-Aminophenyl	272–274[c]	61[i]	$C_{11}H_{17}N_3 \cdot HCl$	58.00	58.34	7.95	7.73
IV	2,4-Dinitrophenyl	233–234[d]	100	$C_{11}H_{14}N_4O_4 \cdot HCl$	43.62	43.33	4.99	4.76
V	α-Naphthylmethyl	244–245[c]	20	$C_{16}H_{20}N_2 \cdot 2HCl$	61.30	61.35	7.09	7.06
VI	2-Lepidyl	dec. over 295	85	$C_{15}H_{19}N_3 \cdot 2HCl$	22.60[k]	22.82[k]		
VII	α-(α-Naphthyl)benzyl	211.5–213[e]	90	$C_{22}H_{24}N_2 \cdot 2HCl$	67.86	67.55	6.74	6.78
VIII	α-(β-Naphthyl)benzyl	219–220[c]	65	$C_{22}H_{24}N_2 \cdot 2HCl$	67.86	67.68	6.74	6.72
IX	4-Phenylbenzhydryl	219.5–220[c]	85	$C_{24}H_{26}N_2 \cdot 2HCl$	69.37	69.18	6.80	6.71
X	4-Phenoxybenzhydryl	203–204[f]	65	$C_{24}H_{26}N_2O \cdot 2HCl$	66.78	66.72	6.54	6.44
XI	α-Phenylphenacyl	227–228[c]	90	$C_{19}H_{22}N_2O \cdot 2HCl$	62.10	61.92	6.59	6.51
XII	α-Phenyl-β-hydroxyphenethyl	233.5–234.5[c]	60	$C_{19}H_{24}N_2O \cdot 2HCl$	61.77	62.06	7.10	7.45
XIII	α-Phenyl-4-hydroxyphenacyl	214–216 (dec.)	65	$C_{19}H_{22}N_2O_2 \cdot 2HCl$	56.85	56.80	6.55	6.72
XIV	9-Phenanthridylmethyl	222–223	80	$C_{19}H_{21}N_3 \cdot 2HCl \cdot 2H_2O$[g]	56.97	57.33	6.80	6.11
XV	2-Chloro-6-methoxyacridyl	290–293[h]	50	$C_{19}H_{20}ClN_3O \cdot 2HCl$	54.98	55.33	5.35	5.68

[a] Melting points below 230° are corrected. [b] Yellow needles. [c] Needles. [d] Yellow prisms. [e] Leaflets. [f] The base melts at 90–90.5°. [g] Cl. Calc'd: 17.74. Found: 17.62. [h] Orange powder. [i] By hydrogenation of II with Adams' catalyst in methanol. Reduction was incomplete probably because of insolubility of the substrate and the product. [k] Chlorine.

until the washings were neutral. The basic material was then extracted from the ethereal layer with dilute hydrochloric acid and the base was liberated by addition of alkali. In a few cases the products could be crystallized as bases from petroleum ether. The general procedure, however, was to dry the base in ethereal solution over potassium carbonate, and transform it to the hydrochloride with ethanolic hydrogen chloride solution. Compounds I–IV were isolated as monohydrochlorides, the rest as dihydrochlorides. These salts were purified by crystallization from methanol or ethanol or from mixtures of those alcohols with ether.

Compound III was prepared by catalytic hydrogenation of II. When Compound XI was hydrogenated with Adams' catalyst, cleavage (debenzylation) resulted. Compound XII was subsequently obtained by reduction of XI with aluminum isopropoxide.

The reaction of trityl chloride with methylpiperazine was also attempted and was probably successful. However, in the step of extraction of basic material with *N* hydrochloric acid, cleavage ensued, and only an additional quantity of methylpiperazine could be found in the aqueous extract. Since *tritylmethylpiperazine* would be of no physiological interest if so easily degraded, no further attempts were made to prepare it.

PREPARATION OF INTERMEDIATES

The *halides* required for Compounds I, II, IV–VI, XI, and XV require no comment. Compound XIV was prepared from 9-chloromethylphenanthridine (5). The substituted benzhydryl chlorides corresponding to Compounds VII–X were prepared by the method of Norris and Blake (6) who described 4-phenoxybenzhydryl chloride and α-naphthylphenylchloromethane. Norris and Banta (7) have reported 4-phenylbenzhydryl chloride. β-Naphthylphenylchloromethane, prepared from the known carbinol, crystallizes from benzene-hexane mixture in colorless needles, m.p. 75.5°.

Anal. Calc'd for $C_{17}H_{13}Cl$: C, 80.76; H, 5.19.

Found: C, 80.78; H, 5.22.

The intermediate for Compound XIII, α-phenyl-4-hydroxyphenacylbromide, was prepared by the method of Weisl (8) but was found to melt at 165–166° (dec.) whereas Weisl gives 108° for the melting point. The composition was confirmed by analysis and the ability to react with methylpiperazine establishes the position of the bromine.

Anal. Calc'd for $C_{14}H_{11}BrO_2$: C, 57.73; H, 3.81.

Found: C, 57.77; H, 3.83.

Methylpiperazine. A preparation of this substance has been published recently from the Cyanamid laboratories (9) which is very similar to that we had worked out. The chief differences are in the reductive methylation step (monocarbethoxypiperazine → N′-methyl-N-carbethoxypiperazine) for which we employed the Clarke-Eschweiler procedure (10), and in the isolation of the base which we accomplished by the addition of sodium methoxide solution to the dihydrochloride followed by fractional distillation of the filtered methanolic solution. This procedure gives about 80% recovery of the base, while most of the remainder, contained in intermediate fractions, can be added to later runs. As the reductive methylation gives 99% of pure carbethoxymethylpiperazine hydrochloride the isolation of this substance can be omitted.

Acknowledgment. The authors wish to express their gratitude to Mr. Samuel Blackman who performed the microanalyses here recorded.

SUMMARY

1. A series of unsymmetrically disubstituted piperazines has been prepared.

2. Antihistaminic activity is manifested fairly generally in the series. When the N′-substituent is methyl, the optimal size for the N-substituent is close to that of a benzhydryl group.

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[Contribution from The Wellcome Research Laboratories]

UNSYMMETRICALLY DISUBSTITUTED PIPERAZINES. III. N-METHYL-N′-BENZHYDRYLPIPERAZINES AS HISTAMINE ANTAGONISTS[1]

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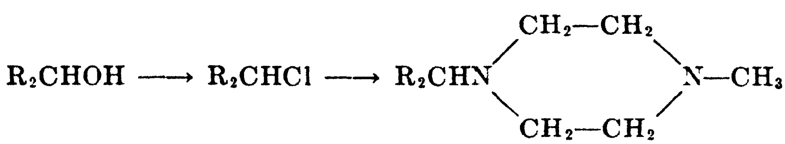
Testing of N-methyl-N′-benzhydrylpiperazine by the tracheal chain method (1, 2) revealed antihistaminic potency almost identical with that of dimethylaminoethyl benzhydryl ether (Benadryl). The toxicity was also very similar. Exploratory experiments reported separately (3) showed that the benzhydryl group was close to the optimal size and that hydrophilic substitution thereon was undesirable. Chief attention was given therefore to variations of the benzhydryl group, the results of which are the subject of this paper.

Synthesis of the benzhydrylmethylpiperazines was along the general line:



Some of the required carbinols were prepared directly from the appropriate aldehydes and Grignard reagents. The others were obtained by reduction of the corresponding ketones.

Quaternization of the methyl-bearing nitrogen atom (Compound II) largely abolished activity. Compounds III and XVIII, in which one phenyl group is replaced by a cyclohexyl radical, also showed diminished potency.

The first substituted benzhydrylmethylpiperazines prepared were Compounds VI, XV, and XVII, having *p*-chloro, *o*-methoxy, and *p*-methoxy substitution respectively. All of these were less toxic than the parent substance, VI being about one-half and XVII about one-third as toxic. Compounds XV and XVII appeared respectively to be slightly less and slightly more potent than I. Compound VI was hard to evaluate by the tracheal chain method since the onset of its action was slow and its action persisted through a number of washings. Tested on live guinea pigs it was found to be very potent and persistent in action, some pigs being protected from histamine shock as long as twenty-four hours. On the other hand, Compound XVII was virtually impotent when tested *in vivo*.

This anomalous behavior of Compound XVII is probably the result of instability since it is rapidly cleaved in warm aqueous and alcoholic solutions to methylpiperazine dihydrochloride and neutral fragments (presumably *p*-methoxybenzhydrol or its ether). In the absence of heat, cleavage is slower and the compound can be purified by careful recrystallization, but dilute aqueous solutions

[1] The work here reported is part of a joint program carried out in collaboration with a pharmacological group in these laboratories.

become turbid within two hours even in the refrigerator. The *o*-methoxy compound, XV, is considerably more stable.

This cleavage is presumably to be written as $R_2CH\overset{+}{N}H< \rightarrow R_2\overset{+}{C}H + HN<$ which is entirely analogous to the cleavage: $(C_6H_5)_2CH\overset{+}{N}Me_3 \rightarrow (C_6H_5)_2\overset{+}{C}H + NMe_3$ studied by Hughes and Ingold (4) and shown to be independent of $[OH^-]$. Such a cleavage is of the same nature as the rate determining step in SN_1 substitutions,[2] which for benzhydryl halides is: $(C_6H_5)_2CHX \rightarrow (C_6H_5)_2\overset{+}{C}H + X^-$.

Norris and co-workers (8, 9, 10) determined alcoholysis rates for a number of benzhydryl halides and showed that methoxy substitution in the *para* position stimulated alcoholysis tremendously.[3] In the *ortho* position the influence of the methoxyl group was much less. Halogen substitution tended to stabilize the benzhydryl halides, most markedly when in the *ortho* position. These findings are in general accord with theoretical expectations.

Since the rates of cleavage of substituted benzhydryl ammonium salts should parallel the rates of alcoholysis of the corresponding benzhydryl halides, it was hoped that compounds with both alkoxyl and halogen substitution in the benzhydryl moiety would be more stable than Compound XVII and might combine the advantages of the two types of substitution. At the same time a variety of benzhydrylmethylpiperazines with halogen substitution in *ortho* and *meta* positions and with several halogen substitutions were prepared. Data on these substances are presented in Table I.

The expectation that halogen substitution would counteract the labilizing effect of methoxyl substitution was partially fulfilled. Compounds XIX–XXVI are considerably more stable than XVII, although cleavage does take place with

[2] Swain (5) has recently shown that the solvolysis of trityl chloride (and very likely of other halides normally considered to be reacting by the SN_1 mechanism) involves solvation of the halogen by a hydrogen-bonding mechanism. Key evidence in this paper is the existence of third-order reaction rates in indifferent solvents and especially the fact that in solutions containing both phenol and methanol solvolysis is first-order with each and much more rapid than with either alone.

The ion $R_2\overset{+}{C}HN<$ might be considered equivalent to $(C_6H_5)_3C—Cl \ldots HOC_6H_5$ of Swain's mechanism, on which basis it would be predicted that cleavage of benzhydrylamine salts in indifferent solvents would be first-order with respect to an alcohol or water present in small amount and would not be affected by added phenol.

Whether these reactions are supposed to proceed by a true ionization or by Swain's mechanism, the effect of electron attracting or repelling substituents on the rates should be the same.

Cantarel (6, 7) has reported certain cleavages of N-substituted benzhydrylamines and their salts. In a qualitative sense the mechanism we suggest can account for the cleavages and the products of secondary reactions he reported but Cantarel informs us that he is not as yet satisfied with a detailed interpretation on this basis.

[3] Norris found the rate for *p*-methoxybenzhydryl chloride about 1200 times that for benzhydryl chloride. The rate determinations of Norris and his group have been criticized rather severely (11, 12, 13), but it is unlikely that their results are seriously in error in respect to the general extent of the larger effects observed.

TABLE I

N-Methyl-N'-Benzhydrylpiperazine Dihydrochlorides

Comp. No.	Benzhydryl Substitution	M.P., °C.*	Empirical Formula	PK_{a1}	PK_{a2}	Analyses, % Carbon Calc'd	Carbon Found	Hydrogen Calc'd	Hydrogen Found
I	None	dec. > 255[a, d]	$C_{18}H_{24}Cl_2N_2$	2.54	7.92	63.72	63.83	7.13	6.88
II	Methochloride hydrochloride	240 (dec.)	$C_{19}H_{26}Cl_2N_2$			64.56	64.37	7.42	7.56
III	1,2,3,4,5,6 hexahydro	249 (dec.)[b]	$C_{18}H_{30}Cl_2N_2$	3.05	8.09	62.57	62.59	8.76	8.38
IV	2-Cl	248	$C_{18}H_{23}Cl_3N_2$	2.38	7.87	57.84	57.72	6.21	6.04
V	3-Cl	250–252	$C_{18}H_{23}Cl_3N_2$	2.39	7.79	57.84	57.46	6.21	6.07
VI	4-Cl	216–216.5[b, e]	$C_{18}H_{23}Cl_3N_2$	2.44	7.78	57.84	57.96	6.21	5.91
VII	2-Br	252 (dec.)[f]	$C_{18}H_{23}BrCl_2N_2$	2.33	7.78	51.68	52.02	5.55	5.80
VIII	4-Br	227–228	$C_{18}H_{23}BrCl_2N_2$	2.43	7.88	51.68	51.53	5.55	5.76
IX	4-Me-4'-Cl	226	$C_{19}H_{25}Cl_3N_2$	2.32	7.78	58.83	59.07	6.50	6.33
X	2,4-Cl_2	233	$C_{18}H_{22}Cl_4N_2$	2.22	7.67	52.94	52.70	5.43	5.06
XI	3,4-Cl_2	237–238.5	$C_{18}H_{22}Cl_4N_2$	2.24	7.65	52.94	52.71	5.43	5.69
XII	4,4'-Cl_2	249[f]	$C_{18}H_{22}Cl_4N_2$	2.33	7.71	52.94	52.82	5.43	5.24
XIII	4-Cl-4'-Br	241–243[g]	$C_{18}H_{22}BrCl_3N_2$	2.27	7.66	47.74	47.66	4.90	4.89
XIV	2,4,4'-Cl_3 monohydrochloride	257–258[a]	$C_{18}H_{20}Cl_4N_2$	2.11	7.46	53.21	53.60	4.97	4.65
XV	2-MeO	196 (dec.)	$C_{19}H_{26}Cl_2N_2O$	2.60	7.93	61.77	61.71	7.10	6.93
XVI	3-EtO	226–228[h]	$C_{20}H_{28}Cl_2N_2O$			62.64	62.48	7.37	7.13
XVII	4-MeO	191–192[a]	$C_{19}H_{26}Cl_2N_2O$	2.44	7.85	61.77	61.88	7.10	6.99
XVIII	4'-MeO-1,2,3,4,5,6,-hexahydro	218 (dec.)	$C_{19}H_{32}Cl_2N_2O$	3.14	8.09	60.77	60.47	8.50	8.40
XIX	2-MeO-5-Cl	225–227[i]	$C_{19}H_{25}Cl_3N_2O$	2.42	7.82	56.50	56.28	6.24	6.02
XX	4 MeO-3-Cl	221 (dec.)	$C_{19}H_{25}Cl_3N_2O$	2.24	7.71	56.50	56.27	6.24	6.10
XXI	4-MeO-4'-Cl	182–184 (dec.)[j]	$C_{19}H_{25}Cl_3N_2O \cdot \frac{1}{2}H_2O$	2.30	7.77	55.26	54.92	6.38	6.57
XXII	4-MeO-3-Br	208.5–209.5	$C_{19}H_{25}BrCl_2N_2O$			50.89	50.42	5.62	5.65
XXIII	4-MeO-2'-Br	211–213 (dec.)[c]	$C_{19}H_{25}BrCl_2N_2O$			50.89	50.82	5.62	5.40
XXIV	4-MeO-2,4'-Cl_2	172[k]	$C_{19}H_{24}Cl_4N_2O$			52.05	52.01	5.52	5.43
XXV	4-MeO-3,4'-Cl_2	210–211.5[k]	$C_{19}H_{24}Cl_4N_2O$			52.05	51.68	5.52	5.79
XXVI	4,4'-$(MeO)_2$-3,3'-Cl_2	225–227[a, l]	$C_{20}H_{26}Cl_4N_2O_2$			51.27	51.27	5.60	5.64

* Melting points below 230° are corrected.
[a] Needles.
[b] Prisms.
[c] Platelets.
[d] M.p. of base, 105.5–107.5°.
[e] The base distills at 137–145° at 0.10–0.15 mm. (bath temperature, 185–197°); at 0.0002–0.0003 mm. pressure it distills from a bath at 90–93°.
[f] M.p. of base, 77–78°.
[g] M.p. of base, 99–101°.
[h] M.p. of base, 75–77°, b.p., 140–150° at 0.03–0.05 mm.
[i] M.p. of base, 124–125°.
[j] M.p. of base, 63–65°.
[k] The base distills at 0.0002–0.0003 mm. from a bath at 140°.
[l] M.p. of base, 99–99.5°.

all of them in aqueous solution. Anti-histaminic activity, however, diminished. Of the methoxy-halogen derivatives, only Compound XXI showed appreciable activity and it was less potent than I. At the same time, examination of the halogenated compounds (IV–XIV) revealed the interesting fact that substitution elsewhere than in the *para* position was not advantageous. Compounds X and XI as well as XX and XXII were less potent than the unsubstituted compound. All the substances having only *para* halogen substitution (VI, VIII, XII, and XIII) manifested the same type of physiological behavior, differences being relatively insignificant.

Two explanations for these findings suggest themselves. The prolonged action of the *para*-halogen derivatives might be due to inhibition of metabolic oxidation, which would probably lead to physiologically inert substances. The other explanation, which is especially reinforced by the observation that repeated washings of the tracheal chains (in the screening tests) do not abolish the effect of these drugs, is that these antihistaminics function by being absorbed on (and blocking the action of) some enzyme whose matrix admits the presence of *para*-substituents only.

The electron-attracting or -releasing effect of these polar substituents ought to be reflected to some extent in the basicity of the benzhydrylmethylpiperazines Electrometric titrations were carried out with about half of the compounds in 50% methanol. The results, expressed as PK_{a1} and PK_{a2} (apparent) for the conjugate acids, are given in Table I. Certain definite trends are evident, although the effect of variations on the basicity of the benzhydrylamino nitrogen tends to be masked by the presence of the more strongly basic methylamino group—itself little affected by substitution in the benzhydryl portion. One halogen substitution (Compounds IV–VIII) diminishes PK_{a1} by 0.1–0.15 PK units. The influence of two or three halogens is greater in about the same ratio.

The influence of methoxyl substitution on PK_{a1} is less than had been expected and is largely negative. The resonance of a methoxyl could be expected to increase electron concentration *para* to itself and thus to increase basicity. This tendency, if present, is of minor importance and the methoxyl seems to function mainly through its inductive action, electron attraction being dominant. This suggests that the methoxyl resonance while important in activated or transition states, has little influence on continuing, unactivated properties of the molecule.

EXPERIMENTAL

The *synthesis* employed by us is not the only one possible but is the most convenient for the preparation of a series. Benzhydryl halides tend to react by the SN_1 mechanism, wherefore hydroxylic solvents must be avoided, and in common non-polar solvents reaction is slow. Monobenzhydrylpiperazines are obtainable by direct reaction of anhydrous piperazine and benzhydryl halides but the operation is far less convenient than that between the halides and methylpiperazine. It is advantageous, though not essential, to use the latter substance in about 100% excess, the unreacted material being subsequently recoverable.

Another objection to the initial preparation of monobenzhydrylpiperazines is that

methylation of the secondary nitrogen by alkylating agents gives poor yields. Reductive methylation carries the risk of removal of the benzhydryl group.[4]

PREPARATION OF INTERMEDIATES

Data on new compounds prepared as intermediates are presented in Table II; melting points are corrected.

Carbinols. The substituted benzhydrols corresponding to Compounds III–VI, IX, and XV–XVIII were obtained from the reactions of phenyl-, *p*-tolyl-, and cyclohexyl-magnesium bromides with the appropriate aldehydes. The other benzhydrols required were prepared by reduction of the corresponding ketones. For this purpose the classical procedure using zinc dust and alcoholic alkali (15) is usually adequate. Ketones containing bromine were reduced by the Meerwein-Ponndorf method to avoid loss of halogen. Ketones having substituents *ortho* to the carbonyl are reduced rather slowly and with these also the Meerwein-Ponndorf method was preferable since the course of the reduction could be followed. The carbinols corresponding to Compounds X, XI, XIV, XX, and XXII–XXV were not crystalline although presumably substantially pure.

Benzophenones. These were prepared by the Friedel-Crafts reaction. Several reactions in this series involving substitution of chloro- and bromo-benzene were found to give poor yields by the usual procedure employing carbon disulfide as solvent. In the preparation of 2,4,4′-trichlorobenzophenone from 2,4-dichlorobenzoyl chloride and chlorobenzene, an excess (3 mols) of the latter was used as solvent. The acid halide was added last, with no temperature control during addition, and the reaction mixture was heated at 80° for an hour thereafter. The yield by this procedure was 90%.

Benzyhydryl chlorides. With one exception the benzhydryl chlorides were prepared by the method of Norris and Blake (10). This procedure was apparently inadequate with the unreactive 2,4,4′-trichlorobenzhydrol, which was accordingly treated with thionyl chloride by the method of Levene and Mikeska (16) (for α-cyclohexylbenzyl chloride). The oily product was reacted directly with methylpiperazine. The neutral fraction from this reaction amounted to 20–25% of the starting carbinol and may be presumed from the odor to have contained sulfur derivatives. Nevertheless, Compound XIV was obtained in 75% yield. The method of Levene and Mikeska would also presumably have given better results than that of Norris and Blake in the preparation of α-cyclohexylbenzyl chloride. The product from the Norris and Blake procedure could be transformed into Compound III in only about a 25% yield. The rather large neutral fraction from this reaction still contained much halogen which was relatively unreactive and is suspected to have been mainly *1-benzyl-1-chlorocyclohexane*.

In all the other preparations the Norris and Blake method appeared to give a nearly quantitative transformation, as judged by the yield of pure benzhydryl chloride or of benzhydrylmethylpiperazine when the chloride was used without purification. Because of the sensitivity of the benzhydryl chlorides they were not subjected to extended manipulations. While many of them undoubtedly could be distilled in a good vacuum this was attempted only with *p*-chlorobenzhydryl chloride, which was known to survive such treatment. With that exception, attempts were made to crystallize the halides from hexane and if these attempts failed, the solvent was evaporated and the oily residue used directly in the next step.

Benzhydrylmethylpiperazines. When the required benzhydryl chloride was available in pure form, 0.02 mole of that substance was added to 0.04 mole of methylpiperazine (3) together with a little benzene to facilitate mixing. When a crude benzhydryl chloride was to be used, a quantity equal in weight to 0.03 mole was taken and 0.06 mole of methylpiperazine. Thereafter the manipulations were identical. Each reaction mixture, covered loosely

[4] *Cf.*, Clarke, Gillespie, and Weisshaus (14) on the reductive methylation of dibenzylamine.

TABLE II

INTERMEDIATES IN THE PREPARATION OF BENZHYDRYLMETHYLPIPERAZINES

COMPOUND[a]	M.P., °C.	APPEARANCE	EMPIRICAL FORMULA	ANALYSES, %			
				Carbon		Hydrogen	
				Calc'd	Found	Calc'd	Found
2,4-$Cl_2C_6H_3COC_6H_4Cl$-4	64–64.5	Needles	$C_{13}H_{17}Cl_3O$	54.66	54.40	2.47	3.00
4-MeO-3-Cl-$C_6H_3COC_6H_5$	82–84	Leaflets or prisms	$C_{14}H_{11}ClO_2$	68.39	68.17	4.46	4.37
4-MeO-2-Cl-$C_6H_3COC_6H_4Cl$-4	68–70	Silky needles	$C_{14}H_{10}Cl_2O_2$	59.79	59.50	3.50	3.72
4-MeO-3-Cl-$C_6H_3COC_6H_4Cl$-4	127.5–128	Silky needles	$C_{14}H_{10}Cl_2O_2$	59.79	59.70	3.50	3.65
4-$ClC_6H_4CHOHC_6H_4Br$-4	103–104	Fine meshed needles	$C_{13}H_{10}BrClO$	52.45	52.60	3.39	3.63
3-$EtOC_6H_4CHOH$-C_6H_5	51.5–52	Needles	$C_{15}H_{16}O_2$	78.91	78.83	7.07	7.16
2-MeO-5-ClC_6H_3CHOH-C_6H_5	70–71.5	Prisms	$C_{14}H_{13}ClO_2$	67.59	67.68	5.27	5.12
4-$ClC_6H_4CHClC_6H_4Br$-4	78	Prisms	$C_{13}H_9BrCl_2$	49.38	49.31	2.87	2.93

[a] All compounds crystallized for analysis from hexane or ether-hexane mixtures.

with a watch-glass, was heated in the steam-bath for 4 to 48 hours, depending on the expected reactivity of the halide. In most cases a deposit of solid, presumably a hydrochloride of methylpiperazine, formed within an hour.

When reaction was believed complete, the flasks were cooled and the contents partitioned between ether and water, the ethereal layers being washed with water until the washings were neutral. The products were then extracted by washing with successive portions of dilute hydrochloric acid until the extracts were strongly acid to Congo Red paper. The ethereal layers, containing only neutral material, were evaporated. The neutral residues usually amounted to less than 1 g. The aqueous solutions were basified and the liberated bases were taken into ether and dried over potassium carbonate. Thereafter procedures varied somewhat. A number of bases could be crystallized from hexane and advantage was taken of this method of purification where possible. Some, perhaps most, of the bases can also be distilled in high vacuum but this was usually unnecessary and distillation was seldom attempted save when other methods failed to give analytically-pure material. Most frequently the base in ethereal solution was poured into ethanol containing an excess of hydrogen chloride.

Most of the *dihydrochlorides* crystallized readily and all could be recrystallized from alcohol or alcohol-ether mixtures. Compound XXV was induced to crystallize only after the base had been distilled, but thereafter behaved normally. Many of the dihydrochlorides came down as fine powders with no grossly visible crystalline form.

In the preparation of Compound XIV, a salt, presumably a *monohydrochloride hydrate*, crystallized during the acid extraction. This salt came out of aqueous solution acid to Congo Red but dissolved in more concentrated acid. It could be crystallized as platelets from water and melted below 112° when immersed in a bath at that temperature. When heated more slowly it sintered at about 103°, gave off gas and did not melt below 200°. It was readily soluble in absolute ethanol at 25° from which solution needle-like crystals separated spontaneously. No other water-insoluble hydrochlorides were encountered but benzhydrylmethylpiperazine itself forms a monohydrochloride with only moderate solubility in water.

Quite a number of the dihydrochlorides offered considerable difficulty in the matter of analysis, apparently due to obstinate retention of water. Compound XXI, for example, appeared to form a hemi-hydrate and gave satisfactory analyses for that composition. The calculated weight (for ½ H_2O) was lost only on drying at 0.0003 mm. Compound XXIII liquefied by absorption of moisture when placed in a vacuum desiccator that contained calcium chloride as the desiccant. The water was removed by evacuation on the oil pump.

Electrometric titrations. These were performed on a Beckmann *p*H meter machine by the usual technique. The solvent was 50% methanol and the concentration was 0.02 molar.

SUMMARY

1. A series of N-methyl-N′-benzhydrylpiperazines has been prepared.

2. A number of these substances, especially those with halogen substitution in the *para* position, show marked activity as histamine antagonists.

3. Those members of the series with methoxyl substitution in the *para* position tend to suffer cleavage when present as the bivalent cations in hydroxylic solvents.

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[Contribution from the Sterling Chemistry Laboratory, Yale University]

SYNTHESIS OF SOME NEW 2-ARYLOXY AND 2-ALKYLOXY PYRIDINES

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Antispasmodic activity of the type exhibited by papaverine and atropine has been demonstrated for a wide variety of materials, with no evidence that such activity is limited to specific structures or configurations. Isoquinoline derivatives, aryl and alkyl amines, and innumerable derivatives of acetic acid have been described as spasmolytic agents.[3]

Studies relating to pyridine compounds as antispasmodics are of recent origin. Winterfeld and Holschneider (1) first indicated possible utility in the pyridine series when they reported on a group of α-pyridyl ketones; one of their materials, α-pyridyl γ-aminopropyl ketone, was said to be active on isolated guinea pig uterus in dilutions of 1:100,000. Krohnke (2) prepared a series of pyridinium 2-ethanols of the type $C_5H_5N(CH_2CHOHR)^+Br^-$ some of which exhibited activity resembling that of papaverine. Amides of the pyridine carboxylic acids have also been investigated (3). Coates and co-workers (4) in their investigation of therapeutic agents of the quinoline series noted that various α-, β-, and γ-pyridylquinolines exhibited some antispasmodic action. Subsequent to the completion of the present study antispasmodic activity was reported for benzyl derivatives of α-aminopyridine (5), and for esters of diphenylacetic acid with some pyridyl alkanols (6). In the latter group 1-(α-pyridyl)-2-ethyl diphenylacetate hydrochloride exhibited 1/16 the activity of atropine.

This investigation was undertaken for the purpose of introducing the α-pyridyl group into compounds so constituted that the final products arising from the syntheses would presumably be physiologically active, particularly antispasmodic or antihistaminic in their action. Ethers of 2-hydroxypyridine were selected as the type of compound to be investigated because they possess the therapeutically important iminoester configuration, $RO\overset{|}{C}{=}N-$, and because the synthesis of such materials was made attractive by the availability of 2-bromopyridine (7, 8). Had the notable antihistaminic properties of the basic ethers of benzhydrol (9) and of α-methyl-α-phenyl-2-pyridinemethanol (10) been known when this project was initiated, there would have been an even more cogent reason for conducting the investigation.

Simple ethers of 2-hydroxypyridine have been described from time to time and

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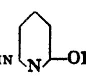
[3] For a comprehensive review of the subject see Blicke, *Ann. Rev. Biochem.*, **13**, 549 (1944).

2-pyridyl ethers of certain amino alcohols were the subject of patents (11, 12). The only pharmacological investigation of such materials was that of Renshaw and Conn (13) in which a series of 2-pyridyl aryl ethers was synthesized and examined for acetylcholine activity. More recently ethers of 2-hydroxy-5-aminopyridine have been described as tuberculostatic agents (14).

The pyridyl ethers obtained directly from 2-bromopyridine are shown in Table I. Ethers of the simple phenols were readily prepared according to the method of Renshaw and Conn (13) by heating 2-bromopyridine and the phenol

TABLE I

2-Pyridyl Ethers

R IN  —OR	B.P./MM.	M.P.[a]	n_D^t	METHOD OF PREPARATION	% YIELD	ANALYSIS, % N	
						CALC'D	FOUND
o-$C_6H_4OCH_3$		91–92		A	71	6.97	7.06
m-$C_6H_4OCH_3$	133–135/1		1.5805^{24}	A	82	6.97	6.96
p-$C_6H_4OCH_3$	152–153/3	42–43		A	82	6.97	6.91
p-$C_6H_4OC_2H_5$	110–111/0.14	45–45.5		A	47	6.51	6.80
p-$C_6H_4OCH_2C_6H_5$		72.5–73		A	43	5.05	5.24
p-C_6H_4Br	122–123/1		1.6072^{23}	B	18	5.60	5.38
$CH(C_6H_5)_2$		57–58		B	53	5.36	5.31
$CH_2C_6H_3(OCH_3)_2$-(3′,4′)		58–59		B	23	5.71	5.74
o-$C_6H_4COOCH_3$		67–68		B	52	6.11	6.03
o-C_6H_4COOH		117–118		[b]	85	6.51	6.48
m-$C_6H_4COOC_2H_5$	143–144/1		1.5614^{25}	A	56	5.76	5.96
m-C_6H_4COOH		125–126		[b]	90	6.51	6.28
p-$C_6H_4COOC_2H_5$		64–65		A	32	5.76	5.85
p-C_6H_4COOH		174		[b]	80	6.51	[c]
$C_{10}H_6COOC_2H_5$(2′,3′)		96–97		B	38	4.78	4.71
$C_{10}H_6COOH$(2′,3′)		149–150		[b]	75	5 28	5.20
$CH_2COOC_2H_5$	83–84/0.5		1.4970^{20}	C	26	7.73	7.50
$CH(CH_3)COOC_2H_5$	113–115/8		1.4901^{23}	C	24	7.18	6.97
$CH(C_6H_5)COOC_2H_5$	135–137/1		1.5515^{18}	C	28	5.45	5.40
$CH(C_6H_5)COOH$		115		[b]	74	6.11	6.20

[a] Corrected.
[b] By saponification of the ester with 10% alcoholic potassium hydroxide.
[c] Neutral equivalent: Calc'd, 216; Found, 215.

in the presence of anhydrous potassium carbonate (Method A). This procedure was also suitable for the preparation of ethers of ethyl *meta*-hydroxybenzoate and ethyl *para*-hydroxybenzoate, but it failed when applied to methyl salicylate and gave a negligible yield with ethyl 2-hydroxy-3-naphthoate. Ethers of these compounds were successfully prepared by heating the appropriate dry sodium phenoxide with 2-bromopyridine in the presence of a catalytic quantity of copper powder (Method B).

In this connection the salutary effect of copper powder should be mentioned. The catalytic action of this substance was particularly notable in the reaction of 2-bromopyridine with the sodium alkoxide of veratryl alcohol; in the absence

TABLE II

PROPERTIES OF AMINOESTERS AND HYDROCHLORIDES

COMPOUND[a]	B.P./MM.	n_D^t	ANALYSIS, % N CALC'D	ANALYSIS, % N FOUND	M.P. OF HCL'D[b]
o-$(C_5H_4N)OC_6H_4COOCH_2CH_2N(C_2H_5)_2$	170–171/1	1.5361^{25}	8.91	8.85	[c]
o-$(C_5H_4N)OC_6H_4COOCH_2CH_2CH_2N(C_2H_5)_2$	179–180/1	1.5364^{26}	8.53	8.49	[c]
m-$(C_5H_4N)OC_6H_4COOCH_2CH_2N(C_2H_5)_2$	169–170/1	1.5200^{27}	8.91	8.91	110–112
m-$(C_5H_4N)OC_6H_4COOCH_2CH_2CH_2N(C_2H_5)_2$	174–175/1	1.5373^{22}	8.53	8.23	129–130
p-$(C_5H_4N)OC_6H_4COOCH_2CH_2N(C_2H_5)_2$	184.5–185.5/1	1.5383^{28}	8.91	8.96	141–142
p-$(C_5H_4N)OC_6H_4COOCH_2CH_2CH_2N(C_2H_5)_2$	187–189/1	1.5353^{28}	8.53	8.48	161–164
2-$(C_5H_4N)OC_{10}H_6$-3-$COOCH_2CH_2N(C_2H_5)_2 \cdot HCl$			6.99	6.95	139–140
2-$(C_5H_4N)OC_{10}H_6$-3-$COOCH_2CH_2CH_2N(C_2H_5)_2 \cdot HCl$			6.75	6.99	150–151
$(C_5H_4N)OCH_2COOCH_2CH_2N(C_2H_5)_2$	103–105/0.14	1.4940^{20}	11.11	11.60	94–96[d]
$(C_5H_4N)OCH_2COOCH_2CH_2CH_2N(C_2H_5)_2$	114–115/0.2	1.4919^{20}	10.52	10.60	[c]
$(C_5H_4N)OCH(CH_3)COOCH_2CH_2N(C_2H_5)_2$	121–123/1	1.4892^{22}	10.53	10.37	[c]
$(C_5H_4N)OCH(CH_3)COOCH_2CH_2CH_2N(C_2H_5)_2$	122–123/0.4	1.4875^{20}	9.99	9.80	[c]
$(C_5H_4N)OCH(C_6H_5)COOCH_2CH_2N(C_2H_5)_2 \cdot HCl$			7.68	7.46	110.5–112
$(C_5H_4N)OCH(C_6H_5)COOCH_2CH_2CH_2N(C_2H_5)_2 \cdot HCl$			7.40	7.22	[c]
o-$(C_5H_4N)OC_6H_4OCH_3 \cdot HCl$			5.89	5.68	158–159
m-$(C_5H_4N)OC_6H_4OCH_3 \cdot HCl$			5.89	5.56	136–139
p-$(C_5H_4N)OC_6H_4OCH_3 \cdot HCl$			5.89	5.57	160–162
p-$(C_5H_4N)OC_6H_4Br \cdot HCl$			4.89	4.88	151–152

[a] (C_5H_4N) = 2-pyridyl.

[b] Dihydrochloride unless otherwise indicated.

[c] Not crystallizable.

[d] Monohydrochloride.

of copper powder the reactants could be heated to 210–220° without evidence of reaction, whereas, when this catalyst was present a vigorous reaction set in at 150°. Unfortunately, the beneficial effect of this reagent was not ascertained until after some of the experimental work had been completed. Thus, it is possible that improved yields could be obtained in some of the cases where copper powder was not employed. Copper powder has been employed in reactions of 2-bromopyridine with amines (15, 16).

2-Pyridyl ethers of ethyl glycollate, ethyl lactate, and ethyl mandelate were prepared through interaction of the sodium alkoxide of the ester with an excess of 2-bromopyridine at 110–120° (Method C). Numerous solvents were tried for this reaction but superior results were secured with 2-bromopyridine itself. When applied to ethyl benzilate, Method C yielded none of the expected ethyl diphenyl-(2-pyridoxy)acetate; instead, a small quantity of material was isolated which proved to be the 2-pyridyl ether of benzhydrol. This compound was prepared in quantity from benzhydrol by Method B and it proved to be identical with the product obtained from the reaction involving ethyl benzilate. It was not possible to prepare ethyl diphenyl-(2-pyridoxy)acetate.

The esters which arose from some of these syntheses were converted to alkamine esters of β-diethylaminoethanol and γ-diethylaminopropanol, respectively. For all but two cases the transformation was accomplished through alcoholysis of the alkyl esters with excess amino alcohol containing a small quantity of dissolved sodium metal. The procedure failed when applied to ethyl phenyl-(2-pyridoxy)acetate and ethyl 2-(2′-pyridoxy)-3-naphthoate, so these esters were converted to the corresponding free acids by saponification, and the acids were reacted with β-diethylaminoethyl chloride and γ-diethylaminopropyl chloride in dry isopropyl alcohol, thus yielding the respective alkamine ester monohydrochlorides. The free bases were not isolated.

Treatment of the alkamine esters with an excess of hydrogen chloride in ether yielded dihydrochlorides which were frequently non-crystallizable hygroscopic oils. In a few instances it was possible to prepare monohydrochlorides by limiting the quantity of hydrogen chloride employed and these materials were sometimes more tractable. Monohydrochlorides of some of the simple ethers were also prepared.

Pharmacological evaluation of these compounds has not been completed, but will be reported elsewhere at a later date.

EXPERIMENTAL

Preparation of 2-pyridyl ethers. As noted in the discussion, three methods of synthesis were employed. Selected examples illustrative of each method are given below.

METHOD A. *Ethyl p-(2-pyridoxy)benzoate.* In a flask fitted with an air condenser a mixture of 7.9 g. (0.05 mole) of 2-bromopyridine, 16.6 g. (0.10 mole) of ethyl p-hydroxybenzoate, and 6.9 g. (0.05 mole) of anhydrous potassium carbonate was heated at 150–160° for six hours. When it had cooled, the gray solid was taken up in 50 ml. of 8% sodium hydroxide and the mixture was extracted several times with 30-ml. portions of ether. The ether extracts were dried over Drierite. Removal of the ether left an oil which, when heated to 120° at 1 mm. pressure, yielded approximately 3 g. of distillate consisting of 2-bromopyridine and some phenolic material. The undistilled residue solidified on cooling and it

was then crystallized from 95% alcohol in the form of fine needles which melted at 63–65°. Two more crystallizations raised the melting point to 64–65°. Yield, 4.0 g.; 32%.

Anal. Calc'd for $C_{14}H_{13}NO_3$: N, 5.76. Found: N, 5.85.

p-(2-Pyridoxy)benzoic acid. A solution of 1.0 g. of the ester in 10 ml. of 10% alcoholic potassium hydroxide was gently refluxed for three hours and then diluted with twice its volume of water. Acidification with dilute hydrochloric acid gave 0.7 g. of a fine white precipitate which, when crystallized from alcohol, melted sharply at 174°.

Anal. Calc'd for $C_{11}H_8NO{\cdot}COOH$: Neutral equivalent, 215.

Found: Neutral equivalent, 216.

METHOD B. *Methyl o-(2-pyridoxy)benzoate.* The sodium salt of methyl salicylate was prepared in a 250-ml. round-bottom flask fitted with a dropping-funnel and a condenser with a calcium chloride tube. Methyl salicylate, 15.2 g. (0.10 mole), was added dropwise to a solution of 2.3 g. (0.1 atom) of sodium in 50 ml. of absolute methanol; the sodium salt precipitated as a white crystalline solid. Excess methanol was distilled off, the last traces being removed under diminished pressure (10 mm.) and at a bath temperature of 120°. The caked solid was then broken up and mixed with 15.8 g. (0.10 mole) of 2-bromopyridine and 0.2 g. of copper powder. An air condenser was attached and the mixture was heated to 185°; at this temperature a vigorous reaction took place and the contents of the flask quickly set to a dark brown solid. The temperature was maintained at 180–190° for an hour. When it had cooled, the melt was broken up and treated with 50 ml. of ether which was then decanted and filtered into a separatory funnel. An equal volume of water was added to the residue in the flask and the resulting solution was filtered into the separatory funnel. Failure to filter the ethereal and aqueous portions invariably led to the formation of a very stable emulsion during the ensuing extraction. The green, aqueous layer was extracted twice more with 30-ml. portions of ether and the combined extracts were dried over Drierite. Following the removal of ether, the residue was distilled and the main fraction, b.p. 132–140°/1 mm., solidified on cooling. Crystallization from 95% alcohol gave the pure ester in the form of long needles, m.p. 67–68°. Yield, 11.9 g., or 52%.

Anal. Calc'd for $C_{13}H_{11}NO_3$: N, 6.11. Found: N, 6.03.

o-(2-Pyridoxy)benzoic acid. This acid was obtained by saponification of the methyl ester with alcoholic potassium hydroxide. It was a white solid which, when crystallized from water, melted at 117–118°.

Anal. Calc'd for $C_{12}H_9NO_3$: N, 6.51. Found: N, 6.48.

METHOD C. *Ethyl phenyl-(2-pyridoxy)acetate.* This reaction was carried out in a 500-ml. three-neck flask equipped with a sealed stirrer, a reflux condenser fitted with a calcium chloride tube, and a dropping-funnel. The sodium alkoxide of ethyl mandelate was prepared by the dropwise addition, during a period of from sixty to ninety minutes, of a solution of 27.0 g. (0.15 mole) of ethyl mandelate in 50 ml. of dry ether to a stirred suspension of 3.45 g. (0.15 mole) of sodium sand in 300 ml. of absolute ether. During this time the reactants were kept under an atmosphere of nitrogen. When all of the ester had been added, the creamy suspension was stirred for an hour to make certain that all of the sodium was consumed. Stirring was suspended and the ether was distilled off during the simultaneous dropwise addition of 84 g. (0.53 mole) of 2-bromopyridine. The ether-free mixture was stirred and heated at 110° for six hours. After it had become cool, the chocolate-colored product was taken up with 100 ml. of saturated salt solution and this mixture was extracted three times with 75-ml. portions of ether. The combined extracts were dried over Drierite. Removal of the ether left a dark oil which was distilled and yielded the following fractions: (a) 71 g., b.p. 80–82° (16 mm.); (b) 3 g., b.p. 71° (18 mm.) to 120° (1 mm.); and (c) 6.8 g., b.p. 125–145° (1 mm.). Fraction (a) was unreacted 2-bromopyridine while (b) contained 2-bromopyridine and ethyl mandelate. Distillation of fraction (c) through a ten-inch Vigreux column gave the pure ethyl phenyl-(2-pyridoxy)acetate; it was a pale yellow oil, b.p. 135–137° (1 mm.); n_D^{20} 1.5515. Yield, 6 g. (28.4% based on the amount of 2-bromopyridine consumed).

Anal. Calc'd for $C_{15}H_{15}NO_3$: N, 5.45. Found: N, 5.40.

Phenyl-2-pyridoxyacetic acid. A solution of 1.0 g. of the ethyl ester in 10 ml. of 10% alcoholic potassium hydroxide was gently refluxed for three hours. Then the cherry red solution was diluted with twice its volume of water and dilute hydrochloric acid was added just to the point of neutrality; at this point the solution was colored yellow but no precipitate had formed. After treatment with decolorizing carbon the solution was cooled and further acidified. In this way 0.7 g. of fine white platelets were obtained. The acid was purified by crystallization from a mixture of benzene and low-boiling petroleum ether; m.p. 115°.

Anal. Calc'd for $C_{13}H_{11}NO_3$: N, 6.11. Found: N, 6.20.

Preparation of aminoesters. The following description illustrates the method.

β-Diethylaminoethyl p-(2-pyridoxy)benzoate. Ethyl *p*-(2-pyridoxy)benzoate, 4.86 g. (0.02 mole), was shaken for ten minutes with a solution of 0.1 g. of sodium metal in 16.4 g. (0.14 mole) of β-diethylaminoethanol; then the mixture was set aside for twelve hours, during which time it turned to a gelatinous mass. The flask was fitted with a short (8 inches) Vigreux column to which was attached a condenser and a receiver fitted with a calcium chloride tube. The mixture was kept in a bath at 160–170° for six hours and occasionally the temperature was raised to 180° in order to force over small amounts of ethyl alcohol which had not distilled at the lower temperature. Excess amino alcohol was then removed by distillation under reduced pressure. The solid grayish-colored residue was partially dissolved in 50 ml. of saturated salt solution and this mixture was extracted with three 30-ml. portions of ether. After being treated with Drierite the extracts were distilled to give 3.45 g. (64%) of a pale yellow oil, b.p. 183.5–184.5° (1 mm.); n_D^{28} 1.5383.

Anal. Calc'd for $C_{18}H_{22}N_2O_3$: N, 8.91. Found: N, 8.96.

Esters of γ-diethylaminopropanol were prepared in the same manner except that the reaction temperature was maintained at 170–180°.

Hydrochlorides. Conversion of the simple phenolic ethers and of the aminoesters to hydrochlorides was accomplished by treatment of an ether solution of the base with a solution of hydrogen chloride in the same solvent. Products varied in physical characteristics, a few being readily crystallizable solids while most were gummy, hygroscopic semisolids which solidified only after prolonged successive treatments with dry ether. Hydrochlorides of the basic esters of phenyl-(2-pyridoxy)acetic acid and 2-(2′-pyridoxy)-3-naphthoic acid were prepared indirectly by the following method.

β-Diethylaminoethyl 2-(2′-pyridoxy)-3-naphthoate. A solution of 6.15 g. (0.23 mole) of 2-(2′-pyridoxy)-3-naphthoic acid and 5.0 g. (0.037 mole) of β-diethylaminoethyl chloride in 40 ml. of dry isopropyl alcohol was refluxed for ten hours under anhydrous conditions. The cold solution was filtered, solvent was removed from the filtrate by evaporation under reduced pressure, and the residual oil was suspended in 50 ml. of dry ether. After two days in the refrigerator the product solidified and was crystallized from a small quantity of isopropyl alcohol; complete precipitation was insured by the addition of dry ether. Yield, 4.2 g. A sample crystallized from acetone as a white, granular, non-hygroscopic solid which sintered at 136° and became clear at 139–140°.

Anal. Calc'd for $C_{22}H_{25}ClN_2O_3$: N, 6.99. Found: N, 6.95.

SUMMARY

A series of new 2-pyridyl aryl and alkyl ethers has been prepared for pharmacological study, particularly as antispasmodic or antihistaminic agents.

Synthesis of 2-pyridyl aryl ethers was achieved by condensing 2-bromopyridine with the given phenol in the presence of anhydrous potassium carbonate or with the sodium phenoxide in the presence of copper powder.

The pyridyl alkyl ethers were prepared by reacting 2-bromopyridine with the appropriate sodium alkoxide; copper powder was an effective catalyst in certain instances.

Esters which arose from several of these syntheses were converted into alkamine esters of β-diethylaminoethanol and γ-diethylaminopropanol.

These new compounds have in common the significant iminoester, $-\mathrm{N}{=}\overset{|}{\mathrm{C}}\mathrm{OR}$, configuration.

New Haven, Conn.

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[Contribution from the Central Research Department, Monsanto Chemical Company]

THE PREPARATION OF 2-THIOPHENEALDEHYDE AND SOME OF ITS DERIVATIVES

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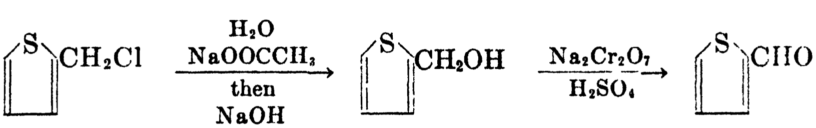
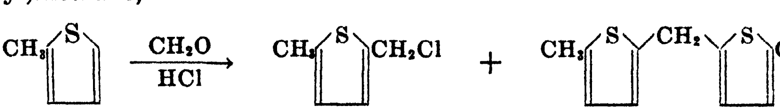
The various methods which have been used for the preparation of 2-thiophenealdehyde recently have been summarized and a new method involving the use of phosphorus oxychloride and N-methylformanilide has been described in detail (1). We also have studied this method and have found that by using benzene or toluene as a solvent the reaction is more readily controlled and the yields are comparable. Besides this method we have examined an alternate route to 2-thiophenealdehyde starting with 2-thenyl chloride and have studied some of the related 2-chlorothiophene and 2-methylthiophene chemistry.

2-Thenyl chloride was hydrolyzed to 2-thenyl alcohol in 77% yield by boiling with aqueous sodium acetate and then with aqueous sodium hydroxide. Since the first step in this hydrolysis yielded an inseparable mixture of the alcohol and acetate, pure samples of both compounds were prepared in order to compare physical properties. These preparations are included in this paper. Boiling a short while with aqueous sodium hydroxide was sufficient to convert the 2-thenyl acetate to 2-thenyl alcohol. Oxidation of the 2-thenyl alcohol with sodium dichromate and sulfuric acid yielded 65% of 2-thiophenealdehyde. When the hydrolysis and oxidation were conducted successively without isolating the intermediate alcohol, the yield of 2-thiophenealdehyde from 2-thenyl chloride was 62%.



5-Chloro-2-thenyl chloride was hydrolyzed to 5-chloro-2-thenyl alcohol in 64% yield by boiling with aqueous sodium acetate and then with aqueous sodium hydroxide. Under the same conditions 5-methyl-2-thenyl chloride yielded 58% of 5-methyl-2-thenyl alcohol. Since the chloromethylation of 2-methylthiophene yielded only 4% of 5-methyl-2-thenyl chloride and 64% of bis-(5-methyl-2-thienyl)methane, the

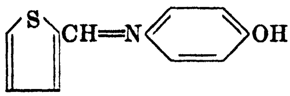


4% 64%

5-methyl-2-thenyl chloride was prepared by reducing 5-methyl-2-thiophenealdehyde with iron and acetic acid (2) (56% yield) and then converting the resulting 5-methyl-2-thenyl alcohol to the chloride by means of thionyl chloride

(71% yield). The chloromethylation of 2-methylthiophene has been described (3), but no yields or properties were given.

With *p*-aminophenol, 6-amino-2-mercaptobenzothiazole, and ethylenediamine, 2-thiophenealdehyde gave the corresponding Schiff bases (I, II, and III) in 93–95% yields.



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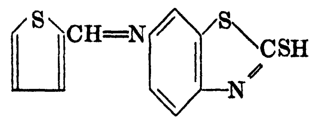

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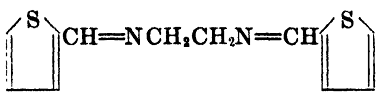
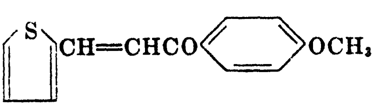


III

The 2-thenal-*p*-aminophenol was reduced to 2-thenyl-*p*-aminophenol in 11% conversion and 22% yield by means of magnesium and methanol (4).

2-Thiophenealdehyde reacted with malononitrile, acetophenone, *p*-methoxyacetophenone, 2,4,6-trinitrotoluene, and rhodanine to give 80–98% of the corresponding 2-thenal derivatives (IV, V, and VI). 2-Thenalacetophenone has been described previously (5, 6), but no details were given for its preparation and the yield was only 67% (5) in contrast to our yield of 96%.



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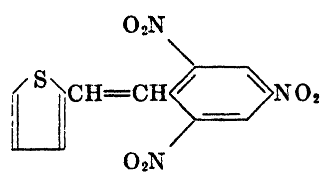
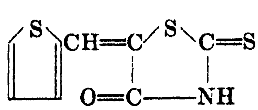
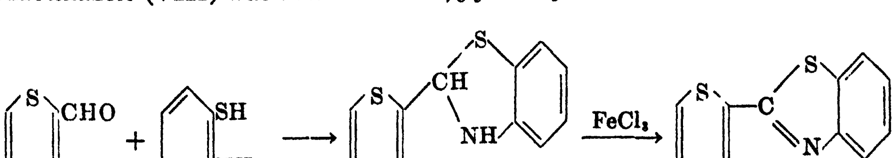


V



VI

With *o*-aminothiophenol, 92% of 2-(2′-thienyl)benzothiazoline (VII) was obtained by the method of Lankelma and Sharnoff (7). The corresponding benzothiazole (VIII) was obtained in 74% yield by oxidation with ferric chloride.



VII VIII

EXPERIMENTAL[1]

2-Thiophenealdehyde. Most of the 2-thiophenealdehyde used in the condensation reactions was prepared by the method recently described in detail by King and Nord, with the modification that a toluene solvent was used. In a 1.5 molar run 300 cc. of anhydrous toluene was employed and the solution was boiled under reflux for one and one-half hours immediately after mixing. The cooled solution was poured on crushed ice, steam-distilled and the product isolated from the distillate. 2-Thiophenealdehyde (b.p. 85–86°/16 mm., n_D^{25} 1.5884) was isolated in 55% conversion and 67% yield.

5-Methyl-2-thiophenealdehyde and 5-chloro-2-thiophenealdehyde were prepared in the same way using benzene as the solvent in 74% and 75% yields, respectively.

2-Thenyl alcohol from 2-thenyl chloride. A vigorously stirred mixture of 66.3 g. of 2-thenyl chloride (8), 82.0 g. of anhydrous sodium acetate, and a trace of a synthetic non-ionic wetting agent in 500 cc. of water was boiled under reflux for one hour. After the mixture was cooled, 30 g. of sodium hydroxide was added and boiling was continued for fifteen minutes. The organic layer was separated from the cooled mixture and the aqueous layer was extracted three times with benzene. The combined organic layer and extracts were dried over potassium carbonate and distilled to give 44.0 g. (77% yield) of 2-thenyl alcohol, b.p. 97–102°/13 mm., n_D^{25} 1.5612.

With such other hydrolytic agents as sodium hydroxide alone, sodium carbonate, sodium bicarbonate, calcium formate, calcium hydroxide, calcium carbonate, and sodium formate the yield of 2-thenyl alcohol fell to 43–61%.

A higher-boiling fraction, obtained in varying amount in each of these hydrolyses, was found to consist largely of 2-thenyl ether. The pure compound boiled at 120–125°/1 mm., m.p. 38–39°.

Anal. Calc'd for $C_{10}H_{10}OS$: S, 30.5. Found: S, 30.1.

2-Thenyl acetate (9). A mixture of 132.5 g. of 2-thenyl chloride, 82.0 g. of anhydrous sodium acetate, and 1.3 g. of triethylamine was stirred vigorously for three hours while heated to 110–120° by means of an oil-bath. The mixture was cooled and filtered The residue was treated with water, and the resulting organic layer was separated and combined with the filtrate. The salt solution was extracted twice with benzene. The combined extracts and organic layer were washed successively with dilute hydrochloric acid, aqueous sodium carbonate, and water. After having been dried over sodium sulfate, the solution was distilled to give, besides benzene, 16.6 g. of forerun, b.p. 81–92°/11 mm., and 107.1 g. (69% yield) of 2-thenyl acetate, b.p. 92–97°/11 mm., n_D^{25} 1.5159. The residue was 15.1 g.

The above 107.1 g. of 2-thenyl acetate was boiled for one and one-half hours with 200 g. of acetic anhydride containing 20 g. of anhydrous sodium acetate. The mixture was poured into water, the layers were separated, and the organic portion was washed successively with three portions of water, one of 2% sodium carbonate, and one of water. After it had been dried over calcium chloride, the product was distilled to give 86.9 g. of product, b.p. 94–96°/12 mm., n_D^{25} 1.5142. This was refractionated through a Lecky–Ewell column to give pure 2-thenyl acetate, b.p. 97.3–97.4°/12 mm., n_D^{25} 1.5140.

Anal. Calc'd for $C_7H_8O_2S$: S, 20.5. Found: S, 20.6.

2-Thenyl alcohol from 2-thenyl acetate. A mixture of 49.3 g. of pure 2-thenyl acetate, 40 g. of potassium hydroxide, and 360 g. of 95% ethanol was boiled under reflux for forty-five minutes. After dilution with 1 l. of water, the solution was saturated with sodium chloride. No oil separated. The solution was extracted five times with benzene. The combined extracts were dried over potassium carbonate and fractionated to give 17.6 g. (49% yield) of 2-thenyl alcohol, b.p. 95.2–96.5°/12 mm., n_D^{25} 1.5630. There was a 4.2 g. residue. An analytical sample boiled at 95.7–96.1°/12 mm., n_D^{25} 1.5630.

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[1] The carbon-hydrogen and nitrogen analyses are microanalyses performed by the Oakwold Laboratories, Alexandria, Virginia and the Micro-Tech Laboratories, 8000 Lincoln Ave., Skokie, Illinois. The sulfur and chlorine analyses were by Mr. Donald Stoltz, Miss Margaret Magin, and Miss Mary Neal, Monsanto Chemical Company, Dayton 7, Ohio.

Anal. Calc'd for C_5H_6OS: S, 28.1. Found: S, 28.0.

2-Thiophenealdehyde from 2-thenyl alcohol. In a 500 cc., three-necked flask equipped with a stirrer, thermometer, and dropping-funnel and cooled by an ice-salt bath was placed 57.0 g. of 2-thenyl alcohol, 150 cc. of acetone, 83.5 g. of sodium dichromate dihydrate, and 50 cc. of water. While this mixture was stirred at 0–5°, a solution of 55 cc. of conc'd sulfuric acid in 26 cc. of water was added over a four-hour period. After another hour at 0–5°, the mixture was poured on to crushed ice and the resulting suspension distilled with steam. The organic layer was separated from the aqueous portion and the latter was extracted twice with benzene. The combined organic layer and extracts were dried over sodium sulfate and fractionated to give 36.5 g. (65%) of 2-thiophenealdehyde, b.p. 79°/12 mm. [77–78°/12 mm. (10)] n_D^{25} 1.5880.

When benzene was substituted for acetone in the above preparation, the mixture became so viscous it was necessary to dilute it further with water. The yield of 2-thiophenealdehyde fell to 46%. A similar oxidation using chromic acid in aqueous acetic acid yielded 58% of 2-thiophenealdehyde.

2-Thiophenealdehyde from 2-thenyl chloride. In a 2-l., three-necked flask equipped with a stirrer, dropping-funnel, and reflux condenser was placed 132.5 g. of 2-thenyl chloride, 123 g. of sodium acetate, 1 l. of water, and a trace of a non-ionic wetting agent. The vigorously stirred mixture was boiled under reflux for one and one-half hours. After it had been cooled to 40°, 50 g. of sodium hydroxide was added slowly. The mixture was then heated slowly to incipient boiling. It was cooled to 50° and a solution of 110 g. of sodium dichromate in 500 cc. of water was added all at once. While the temperature was held at 40–50°, 200 cc. of 50% sulfuric acid was added over a thirty-minute period. The mixture was heated to boiling and steam-distilled. After the organic layer was separated, the aqueous portion of the distillate was extracted three times with benzene. The combined organic layer and extracts were dried over sodium sulfate and fractionated through a Lecky-Ewell column to give 69.2 g. (62%) of 2-thiophenealdehyde, b.p. 86–87°/17 mm., n_D^{25} 1.5884.

When sodium carbonate was substituted for the sodium acetate and sodium hydroxide in the above experiment, the yield of 2-thiophenealdehyde fell to 48%. Direct oxidation of 2-thenyl chloride with aqueous sodium dichromate gave only 35% of the aldehyde. The yield was increased to 47% when sulfuric acid also was added following the addition of 2-thenyl chloride to the dichromate solution.

5-Chloro-2-thenyl alcohol. A vigorously stirred mixture of 50.1 g. of 5-chloro-2-thenyl chloride, 49.2 g. of anhydrous sodium acetate, a trace of a synthetic non-ionic wetting agent, and 300 cc. of water was boiled under reflux for one hour. The mixture was cooled and 30 g. of sodium hydroxide was added. After boiling for another thirty minutes, the mixture was cooled again. The layers were separated and the aqueous layer was extracted three times with benzene. The combined extracts and organic layer were dried over sodium sulfate and distilled to give 28.3 g. (64% yield) of 5-chloro-2-thenyl alcohol, b.p. 121–126°/15 mm., n_D^{25} 1.5695, and 10.8 g. (26% yield) of 5-chloro-2-thenyl ether, b.p. 205–208°/14 mm., n_D^{25} 1.5907. Pure 5-chloro-2-thenyl alcohol boiled at 116°/12 mm., n_D^{25} 1.5714, d_{25}^{25} 1.3658. The compound decomposed with the loss of water before a combustion analysis could be performed.

Anal. Calc'd for C_5H_5ClOS: M_D, 36.5. Found: M_D, 35.8.

Pure 5-chloro-2-thenyl ether boiled at 147–148°/1.5 mm., n_D^{25} 1.5952, d_{25}^{25} 1.3896.

Anal. Calc'd for $C_{10}H_8Cl_2OS_2$: Cl, 25.4. Found: Cl, 25.1.

Bis-(5-methyl-2-thienyl)methane. In a 2-l., three-necked flask equipped with a stirrer, thermometer, and dropping-funnel and cooled by an ice-salt bath was placed 294 g. of 2-methylthiophene. While this was stirred at −2° to −7°, there was added over a two-hour and twenty-minute period a solution of 90 g. of paraformaldehyde in 750 cc. of conc'd hydrochloric acid. The mixture was stirred for twenty minutes longer at the same temperature, diluted with 125 cc. of water, and the layers then were separated. The aqueous layer was extracted three times with chloroform and the combined extracts and organic layer were dried over sodium sulfate. Fractionation yielded, in addition to chloroform, 18.7 g. (4%) of 5-methyl-2-thenyl chloride, b.p. 79–83°/10 mm., n_D^{25} 1.5531; 9.0 g. of intermediate, b.p. 83°/10 mm.–122°/1.5 mm., n_D^{25} 1.5583; and 199.1 g. (64%) of bis-(5-methyl-

2-thienyl)methane, b.p. 122°/1.5 mm.–130°/2 mm., n_D^{25} 1.5818. The residue weighed 86.6 g. The product solidified on standing. A sample, after two crystallizations from ethanol, melted at 38.5–39.0°.

Anal. Calc'd for $C_{11}H_{12}S_2$: S, 30.8. Found: S, 30.4.

5-Methyl-2-thenyl alcohol. A vigorously stirred mixture of 33.4 g. of 5-methyl-2-thiophenealdehyde, 165 g. of iron powder, 275 cc. of glacial acetic acid, 280 cc. of water, and 2 g. of nickelous chloride hexahydrate was boiled under reflux for two and one-half hours. The hot mixture was distilled with steam. The distillate, comprising about 1200 cc., was made alkaline with a slight excess of sodium hydroxide and heated to the boiling point with stirring. Upon cooling, it was extracted four times with benzene. The combined benzene extracts were filtered, washed with water, and dried over potassium carbonate. Distillation yielded 18.8 g. (56%) of 5-methyl-2-thenyl alcohol, b.p. 106–111°/13 mm., n_D^{25} 1.5475.

5-Methyl-2-thenyl chloride. To a well-stirred solution of 18.8 g. of 5-methyl-2-thenyl alcohol in 75 cc. of benzene was added over a ten-minute period, with sufficient cooling to keep the temperature below 30°, 30 g. of thionyl chloride. The mixture was stirred fifteen minutes longer at 20–25° and then distilled to give 15.4 g. (71%) of 5-methyl-2-thenyl chloride, b.p. 83–84°/14 mm., n_D^{25} 1.5510.

Anal. Calc'd for C_6H_7ClS: Cl, 24.2. Found: Cl, 24.7.

5-Methyl-2-thenyl alcohol from 5-methyl-2-thenyl chloride. A mixture of 13.3 g. of 5-methyl-2-thenyl chloride, 20 g. of sodium acetate, and 100 cc. of water was stirred under reflux for forty-five minutes. It was then cooled, 5 g. of sodium hydroxide was added, and the stirring under reflux was continued for fifteen minutes. The mixture again was cooled and extracted four times with benzene. The combined extracts were washed with water and dried over potassium carbonate. Distillation yielded 6.8 g. (58%) of 5-methyl-2-thenyl alcohol, b.p. 106–110°/13 mm., n_D^{25} 1.5479. An analytical sample boiled at 105–106°/12 mm., n_D^{25} 1.5471, d_{25}^{25} 1.1409.

Anal. Calc'd for C_6H_8OS: S, 25.0. Found: S, 25.0.

2-Thenal-p-aminophenol. To a solution of 27.5 g. of *p*-aminophenol in 200 cc. of ethanol was added 28.3 g. of 2-thiophenealdehyde. This mixture was boiled under reflux for fifteen minutes with vigourous stirring. The heating was discontinued and the mixture was stirred an additional fifteen minutes. It was then cooled and left in the refrigerator overnight. The tan crystals were separated by filtration, washed twice with 50% ethanol and dried in a vacuum desiccator over potassium hydroxide. The yield was 48.3 g. (94%), m.p. 203–204°. A sample, after three recrystallizations from ethanol, melted at 204–205°.

Anal. Calc'd for $C_{11}H_9NOS$: N, 6.89. Found: N, 7.05.

2-Thenyl-p-aminophenol. In a 2-l., three-necked flask fitted with a stirrer, thermometer, and bulb reflux condenser was placed 30.5 g. of 2-thenal-*p*-aminophenol, 18.0 g. of magnesium turnings, and 750 cc. of methanol which had been dried over magnesium and then distilled. This mixture was stirred vigorously. The reaction was slow at first. When the temperature rose to 32°, the mixture was cooled occasionally by means of an ice-bath. As the reaction became more vigorous with considerable foaming (after twenty minutes), it was necessary to apply the ice-bath continuously to keep the temperature at 30–32°. One hour after the start of the reaction all of the magnesium had dissolved. Then about 500 cc. of methanol was distilled and the residue was poured slowly into 500 cc. of vigorously stirred 5% aqueous sodium hydroxide cooled by an ice-bath. The resulting greenish-brown slurry was diluted with another 250 cc. of 5% sodium hydroxide and filtered. The gelatinous residue was triturated with a further 150 cc. of 5% sodium hydroxide and filtered. After the combined filtrates had been saturated with carbon dioxide, the resulting light tan precipitate was separated by filtration, washed once with water, and dried. It weighed 12.8 g., m.p. 169–185° and was later shown to be recovered 2-thenal-*p*-aminophenol. On cooling the filtrate 3.3 g. (11% conversion, 22% yield) of crude 2-thenyl-*p*-aminophenol was obtained, m.p. 99–102°. An analytical sample was obtained after four recrystallizations from 40–60% methanol, m.p. 107–108°.

Anal. Calc'd for $C_{11}H_{11}NOS$: C, 64.3; H, 5.40.

Found: C, 64.3; H, 5.33.

The crude first precipitate was recrystallized from 95% ethanol, m.p. 194–200°. It was mixed with an authentic sample of 2-thenal-*p*-aminophenol (m.p. 204–205°) and the melting point again determined; m.p. 202–203°. An additional 2.8 g. of 2-thenal-*p*-aminophenol, m.p. 185–190°, was obtained by reworking the original precipitate of magnesium salts, which brought the recovery to 15.6 g. (51%).

2′-Thenal-6-amino-2-mercaptobenzothiazole. A mixture of 1.1 g. of 2-thiophenaldehyde, 1.8 g. of 6-amino-2-mercaptobenzothiazole, and 25 cc. of absolute ethanol was boiled under reflux for one and one-half hours. Another 25 cc. of ethanol was added and the slurry was filtered while hot. The residue was washed twice with ethanol and dried. The crude 2′-thenal-6-amino-2-mercaptobenzothiazole weighed 2.3 g.; m.p. 254–255° (dec.). An additional 0.2 g. which separated from the cooled filtrates brought the yield to 2.5 g. (93%). The entire product was crystallized three times from pyridine, m.p. 255–256° (dec.).

Anal. Calc'd for $C_{12}H_8N_2S_3$: N, 10.14. Found: N, 9.91.

Di-(2-thenal)ethylenediamine. A mixture of 33.6 g. of 2-thiophenealdehyde, 13.1 g. of 69% ethylenediamine, and 100 cc. of benzene was boiled for thirty minutes under a 1-ft. helices-packed column surmounted by a Dean and Stark trap. The theoretical 9.5 cc. of water was collected in twenty minutes. After 60 cc. of benzene had been distilled, the residual solution was cooled and the resulting mush of crystals diluted with 200 cc. of hexane. The crude di-(2-thenal)ethylenediamine was separated by filtration, washed with hexane, and dried over potassium hydroxide in a vacuum desiccator. The main crop weighed 34.4 g., m.p. 88–90°. An additional 1.1 g., m.p. 84–88°, was obtained from the combined cooled filtrates, which brought the total yield to 35.5 g. (95%). A small sample of the first crop was crystallized twice from benzene-hexane, m.p. 90–91°.

Anal. Calc'd for $C_{12}H_{12}N_2S_2$: N, 11.3. Found: N, 11.1.

2-Thenalmalononitrile. A mixture of 11.2 g. of 2-thiophenealdehyde, 6.6 g. of malononitrile, and 100 cc. of absolute ethanol was heated to boiling. After the addition of two drops of piperidine, the heating was continued for an additional five minutes. Upon cooling, the orange crystals were separated by filtration and dried. The yield was 13.4 g., m.p. 97–98°. An additional 2.2 g., m.p. 95–97°, which was obtained by diluting the filtrate with water, raised this yield to 15.6 g. (97%). The first crop was recrystallized twice from 75% ethanol, m.p. 97–98°.

Anal. Calc'd for $C_8H_4N_2S$: S, 20.0. Found: S, 20.0.

2-Thenalacetophenone. To a solution of 13.2 g. of sodium hydroxide in 120 cc. of water and 60 cc. of ethanol held at 12° by means of an ice-bath was added with vigorous stirring 31.2 g. of acetophenone. There was then added 29.0 g. of 2-thiophenealdehyde and the mixture was stirred at 25° for three hours. The resulting oil, after standing in the ice box for two days, crystallized. The yellow crystals were separated by filtration, washed free of alkali with water, washed with 100 cc. of 50% ethanol and dried in a vacuum desiccator over potassium hydroxide. The yield was 53.4 g. (96%), m.p. 52–58°. After four crystallizations from ethanol, an analytical sample melted at 59° [59° (5, 6)].

Anal. Calc'd for $C_{13}H_{10}OS$: C, 72.9; H, 4.70.

Found: C, 72.8; H, 4.74.

2-Thenal-p-methoxyacetophenone was prepared in the same way from 28.0 g. of 2-thiophenealdehyde, 37.5 g. of *p*-methoxyacetophenone, and a solution of 13.2 g. of sodium hydroxide in 120 cc. of water and 60 cc. of ethanol. The crude product weighed 59.6 g. (98% yield), m.p. 104–106°. A sample was recrystallized twice from ethanol, m.p. 106–107°.

Anal. Calc'd for $C_{14}H_{12}O_2S$: C, 68.8; H, 4.95.

Found: C, 68.7; H, 4.94.

1-(2-Thienyl)-2-(2,4,6-trinitrophenyl)ethylene. A mixture of 11.2 g. of 2-thiophenealdehyde, 22.7 g. of 2,4,6-trinitrotoluene, 1 cc. of piperidine, and 100 cc. of xylene was boiled under reflux while the evolved water was collected in a Dean and Stark trap. After fifteen minutes, when 1.9 cc. of water had collected, the solution was cooled. The resulting mass of crystals was diluted with 25 cc. of benzene, cooled and filtered. More product was obtained by diluting the filtrate with hexane and cooling. The precipitates were combined and dissolved in 200 cc. of benzene. The solution was treated with Norit, filtered while hot, diluted

with an equal volume of hexane and cooled. The resulting orange crystals, which were separated by filtration and dried, weighed 21.0 g., m.p. 134–136°. The additional 0.7 g., m.p. 125–131°, which was obtained by diluting the filtrate with hexane brought the total crude yield of the mixed *cis* and *trans* isomers of 1-(2-thienyl)-2-(2,4,6-trinitrophenyl)ethylene to 21.7 g. (68%). A sample of this crude product was crystallized successively from benzene-hexane, benzene, ethanol, and glacial acetic acid; m.p. 132–141°.

Anal. Calc'd for $C_{12}H_7N_3O_6S$: N, 13.08. Found: N, 13.14.

When this experiment was repeated using benzene as the solvent the time required for the production of the theoretical quantity of water was increased to five hours, but the yield rose to 27.2 g. (85%), m.p. 132–142°.

5-(2'-Thenal)-4-keto-2-thiazolinethione. A mixture of 12.3 g. of rhodanine (11), 10.3 g. of 2-thiophenealdehyde, 20 g. of anhydrous sodium acetate, and 100 cc. of glacial acetic acid was boiled under reflux for twenty minutes. Upon cooling, 250 cc. of water was added and the precipitate was separated by filtration, washed with water, and dried *in vacuo* over potassium hydroxide. The orange crystals of 5-(2'-thenal)-4-keto-2-thiazolinethione weighed 16.8 g. (80%), m.p. 227–232°. A sample was crystallized twice from glacial acetic acid, m.p. 232–233°.

Anal. Calc'd for $C_8H_5NOS_3$: S, 42.3. Found: S, 43.2.

2-(2'-Thienyl)benzothiazoline. To a stirred solution of 31.3 g. of *o*-aminothiophenol in 75 cc. of pyridine was added in a thin stream 28.0 g. of 2-thiophenealdehyde. This mixture was stirred at 85–95° for one-half hour, cooled by means of an ice-bath, and acidified with dilute hydrochloric acid. The oil which separated soon solidified. It was separated by filtration, washed with water and dried *in vacuo* over potassium hydroxide and sulfuric acid. The crude yield of 2-(2'-thienyl)benzothiazoline was 50.4 g. (92%), m.p. 73–86°. A sample, after three crystallizations from ethanol in a carbon dioxide atmosphere, was dried *in vacuo* over potassium hydroxide and sulfuric acid, m.p. 95°.

Anal. Calc'd for $C_{11}H_9NS_2$: C, 60.2; H, 4.14.
Found: C, 60.5; H, 3.90.

2-(2'-Thienyl)benzothiazole. To a stirred solution of 31.5 g. of 2-(2'-thienyl)benzothiazoline in 200 cc. of warm ethanol, was added over a one-half hour period a solution of 26 g. of ferric chloride in 50 cc. of ethanol. The mixture was warmed for another half hour, diluted with 100 cc. of water, and cooled. The thick slurry was diluted with another 300-cc. portion of water and filtered. The residue was washed with water and dried *in vacuo* over potassium hydroxide and sulfuric acid. This crude 2-(2'-thienyl)benzothiazole weighed 23.4 g. (74%), m.p. 95–97°. A sample was crystallized twice from ethanol, m.p. 98–99°.

Anal. Calc'd for $C_{11}H_7NS_2$: C, 60.8; H, 3.25.
Found: C, 61.1; H, 3.41.

SUMMARY

A new route to 2-thiophenealdehyde from 2-thenyl chloride has been examined along with some related 2-chlorothiophene and 2-methylthiophene chemistry.

The attempted chloromethylation of 2-methylthiophene yielded 64% of bis-(5-methyl-2-thienyl)methane.

Three Schiff bases were prepared from 2-thiophenealdehyde in 93–95% yields. 2-Thiophenealdehyde reacted with five compounds containing active methyl or methylene groups to give an 80–98% yield of the corresponding 2-thenal derivatives.

With *o*-aminothiophenol, 2-thiophenealdehyde yielded 92% of 2-(2'-thienyl)-benzothiazoline. The corresponding benzothiazole was obtained in 74% yield by oxidation with ferric chloride.

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[COMMUNICATION No. 1252 FROM THE KODAK RESEARCH LABORATORIES]

3-PHENYLCATECHOL AND RELATED SUBSTANCES

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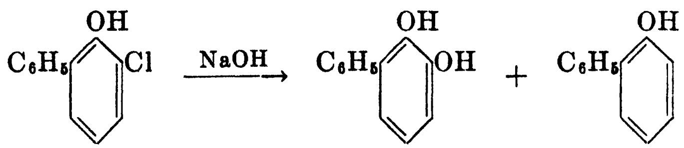
All the homonuclear dihydroxybiphenyls except the 2,3-dihydroxy derivative, 3-phenylcatechol, have been described in the literature.[1] Since this substance appeared to be of interest in connection with other work, its preparation was undertaken.

The reaction employed was alkaline fusion of 2-chloro-6-phenylphenol, essentially by the patented procedure (5), using a mixture of aqueous sodium and barium hydroxides. Upon vacuum-distillation of the reaction product, after acidification, two fractions in about equal amount were collected. The lower-boiling fraction proved to be *o*-phenylphenol, while the higher-boiling one was the expected 3-phenylcatechol. The reaction, thus, proceeds according to the outline.



The replacement of halogen by hydrogen in alkaline fusions is not uncommon; it is called reduction (9).

In view of the unexpected formation of so much *o*-phenylphenol, a similar fusion of 3-bromo-4-hydroxybiphenyl was carried out. The crude material likewise consisted of two fractions, but in very unequal portions; the lower-boiling fraction (approximately one-eighth of the material) was 4-hydroxybiphenyl, while the higher-boiling one was 4-phenylcatechol. It was not possible to separate completely the 4-phenylcatechol from the 4-hydroxybiphenyl by recrystallization. Although the melting points of the catechol and its diacetate were close to that recorded in most of the literature, a single recrystallization of the diacetate raised its melting point fifteen degrees. Furthermore, regeneration of the dihydroxy compound by hydrolysis gave a 4-phenylcatechol with a good melting point, lower than that recorded in the literature. The various melting points of the catechol and its diacetate are collected in Table I.

After this work had been completed, an abstract of a paper by Abe (1) appeared;[2] on consulting the original article, it was found that he, too, recorded the higher melting point for the diacetate and the lower for the catechol, and that his values were in complete agreement with ours. By Abe's method of preparation there was no possibility of contamination with 4-phenylphenol; hence these values must be regarded as correct.

[1] The isomers are 3,4-(4-phenylcatechol) (1, 5, 8); 2,4- (9); 2,5- (3); 2,6- (7); and 3,5- (9).

[2] This abstract is entirely erroneous. A correct abstract appears in *Chem. Abstr.*, **43**, 2181 (1949).

The properties of all the monohydroxy- and homonuclear dihydroxybiphenyls, and related substances, are collected in Table II.

TABLE I

MELTING POINTS OF 4-PHENYLCATECHOLS AND THEIR DIACETATES

SOURCE	CATECHOL, °C.	DIACETATE, °C.
Norris, *et al.* (8)	136–136.5	77–77.5
Harvey (5)	144.8–145.2	77.5–78
Our Crude	146–148	75–77
Our Pure	139–140	90.5–91.5
Technical grade	147–149	—
Abe (1)	141	92

TABLE II

PROPERTIES OF HYDROXYBIPHENYLS AND RELATED SUBSTANCES

SUBSTANCE	M.P., °C.	B.P., °C.	M.P., °C. DIACETATE	M.P., °C. DIBENZOATE
2,3-Dihydroxybiphenyl (3-Phenylcatechol)	113–114	325–328/746	78–79	88–89
3,4-Dihydroxybiphenyl (1, 5, 8) (4-Phenylcatechol)	139–140	363–366/755	90.5–91.5	96–97
2,4-Dihydroxybiphenyl (9)	145	—	—	—
2,5-Dihydroxybiphenyl (3)	96	—	73	—
2,6-Dihydroxybiphenyl (7)	138.5	—	—	—
3,5-Dihydroxybiphenyl (9)	157–158	—	—	—
2-Phenylphenol	57–58	260–263/762 142–144/10	63–64	71–72
3-Phenylphenol (6)	78	—	34–34.2 (11)	—
4-Phenylphenol	159–160	310–314/752	88–89	150

EXPERIMENTAL

Starting materials. (a) *2-Chloro-6-phenylphenol.* The available "Practical" grade of this substance, m.p. 67–71°, evolved hydrogen chloride upon distillation (b.p. 275–278°/762 mm.) and left a residue. However, after one redistillation, followed by a crystallization from ligroin (b.p. 90–120°), it formed pure white plates, m.p. 75–76°.

(b) *3-Bromo-4-hydroxybiphenyl.* This was obtained by following the published procedure (2).

3-Phenylcatechol. A mixture of 204.5 g. (1 mole) of 2-chloro-6-phenylphenol, 120 g. (3 moles) of sodium hydroxide, 315 g. (1 mole) of barium hydroxide octahydrate, 5 g. of copper sulfate (4), and 480 ml. of water was placed in a shaking autoclave and heated to 135°. Shaking was then started, and the temperature was raised to 260–270°, at which point it was kept for ten hours. After cooling to room temperature, the semi-solid contents of the bomb were transferred to a 4-liter beaker and rinsed with water. The combined rinsings and product were then acidified (to Congo Red paper) with concentrated hydrochloric acid, boiled one-half hour, chilled, and extracted with two 500-ml. portions of benzene. The solvent was evaporated and the residue distilled *in vacuo* from a flask having a fractionating sidearm. Two fractions were collected; the lower-boiling portion came over at

135–155°/10 mm. (69 g., 41%) and the higher-boiling one at 155–185°/10 mm. (61 g., 33%). On redistillation of the first fraction at atmospheric pressure, 63 g. (37%) was collected at 260–265°/759 mm.; the solid distillate was then recrystallized from ligroin; it melted at 57–58°, and there was no depression on admixture with an authentic specimen of *o-phenylphenol.*

The second fraction was also redistilled at atmospheric pressure, b.p. 325–328°/746 mm. (175–178°/10 mm.); the yield was 57 g. (30.6%), m.p. 111–113°. On further purification by recrystallization from ligroin, the melting point was raised to 113–114°. *3-Phenylcatechol* is very sparingly soluble in water.

Anal. Calc'd for $C_{12}H_{10}O_2$: C, 77.3; H, 5.4.

Found: C, 77.0; H, 5.7.

4-Phenylcatechol. This substance was obtained by the procedure used for the 3-phenyl isomer, but heating for about ten hours at 180–185°. The two fractions were collected at 170–185°/11 mm. (18.3 g., 17%; m.p. 153–156°) and 185–208°/13 mm. (133 g., 72%; m.p. 136–139°). Upon redistillation at atmospheric pressure, the first fraction gave 14 g. (8.2%) of *p-phenylphenol,* m.p.[3] 159–160°; b.p. 310–314°/752 mm. There was no depression of the melting point on admixture with a specimen of authentic *p*-phenylphenol (4-hydroxybiphenyl).

The second fraction was redistilled and the main product was collected at 358–367°/752 mm.; m.p. 138–140°, in a yield of 126 g. (67.7%). There was no decomposition during any of the distillations. After one recrystallization from xylene, the melting point was 139–140°.

Anal. Calc'd for $C_{12}H_{10}O_2$: C, 77.4; H, 5.4; O, 17.2.

Found: as prepared: C, 77.8; H, 5.6; O, 17.0.

Found: regenerated from diacetate: C, 77.2; H, 5.3.

Other boiling points are 363–366°/755 mm.; 203–205°/13 mm. The product of Norris (8) had a boiling point above 360°, and hence it was largely the *4-phenylcatechol.*

4-Phenylcatechol is soluble in xylene and in warm water, sparingly soluble in ligroin (b.p. 90–120°), but very soluble in methanol and benzene. This distilled product appears to contain a trace of 4-hydroxybiphenyl, judging from the high carbon content. The substance regenerated from analytically pure diacetate gives the correct analysis.

Attempts to prepare 4-phenylcatechol by an Elbs persulfate oxidation (10) of 4-phenylphenol were unsuccessful; most of the phenol was recovered unchanged.

Esters. (a) *4-Phenylcatechol diacetate.* To a solution of 90 g. of 4-phenylcatechol and 450 ml. of acetic anhydride there was added a few drops of concentrated sulfuric acid. The solution became warm and darkened in color. After standing for one-half hour, it was poured into 1 liter of ice water, with rapid stirring. After standing one to two hours, the solid was collected on a filter, washed, and air-dried. The yield was 126 g. (96%), m.p. 74.5–77°. A single recrystallization from 150 ml. of benzene (to which 450 ml. of petroleum ether, b.p. 35–55°, was subsequently added) gave 113.5 g. (90% recovery), with the melting point, 90–91.5°. The melting point was unchanged by a second similar recrystallization, but was very slightly raised (m.p. 90.5–91.5°) by the use of 95% ethanol.

Anal. Calc'd for $C_{16}H_{14}O_4$: C, 71.1; H, 5.2.

Found: C, 71.0; H, 5.3.

Hydrolysis to regenerate 4-phenylcatechol was accomplished by refluxing for one hour a mixture of 90 g. of the diacetate, 180 ml. of 20% hydrochloric acid, and 200 cc. of alcohol. On pouring into cold water with vigorous stirring, beautiful white plates formed; they were washed, and dried at 45° (temperature in drying cabinet). The product melted at 137–139°, with a slight sintering at 136°. The yield was 58 g. (93.5%). It was recrystallized from benzene and petroleum ether, as described above, to obtain an analytical sample.

(b) *4-Phenylcatechol dibenzoate.* A mixture of 90 g. of 4-phenylcatechol, 200 ml. of dioxane, 90 ml. of pyridine, and 155 g. (127 ml.) of benzoyl chloride, was warmed on the steam-bath for fifteen minutes and then cooled by adding ice and 1.5 liters of water. An

[3] After one recrystallization from xylene.

oil separated, which was partially solid the next day; on stirring, it solidified and was collected on a filter. The yield was 197.5 g., m.p. 84–92°. It was dissolved in 250 ml. of absolute ethanol, decolorized by Norit, allowed to crystallize, and collected as before; the recovery was 167 g. (87.5%), m.p. 94.5–96°, with previous shrinking at 93°. The crystallization was repeated, the product melting at 96–97°; a repetition gave an ester, m.p. 96–96.5°, which was unchanged on recrystallization from ligroin (b.p. 65–90°) or isopropyl alcohol.

Anal. Calc'd for $C_{26}H_{18}O_4$: C, 79.2; H, 4.6.

Found: C, 79.2; H, 4.6.

The *dibenzoate* tends to oil out from alcoholic solutions, and it is often advantageous to inoculate the solution with a little of the solid ester.

Hydrolysis of the dibenzoate, to regenerate 4-phenylcatechol, was accomplished by suspending 5 g. of the ester in 20 ml. of methanol, adding a solution of 1.67 g. of 85% potassium hydroxide in 10 ml. of methanol, and swirling, which resulted in complete solution of the ester. The odor of methyl benzoate became noticeable. After ten minutes, the solution was poured into water, and the ester extracted with ether. A little sodium hydrosulfite was added to lighten the color of the aqueous layer, after which it was acidified by addition of concentrated hydrochloric acid. The yellow oil that separated was seeded with a bit of 4-phenylcatechol, but considerable manipulation was required before satisfactory crystallization was achieved. The crude product, isolated in a yield of 74%, melted at 134–137° with previous sintering; however, on recrystallization from benzene, it melted at 137.5–138°, and a mixed melting point was not depressed.

(c) *3-Phenylcatechol diacetate.* This was prepared by the same procedure as that for the 4-isomer. It may be recrystallized from ligroin (b.p. 90–120°) or alcohol. It melts at 79–79.5°; a mixed melting point with the 4-isomer is 62–70°.

Anal Calc'd for $C_{16}H_{14}O_4$: C, 71.1; H, 5.2.

Found: C, 71.1; H, 5.2.

(d) *3-Phenylcatechol dibenzoate* was likewise prepared by the Einhorn procedure. It has m.p. 89° after recrystallization from ligroin or alcohol; the mixed melting point with the 4-isomer is 75–80°.

Anal. Calc'd for $C_{26}H_{18}O_4$: C, 79.2; H, 4.6.

Found: C, 79.3; H, 4.2.

(e) *o-Phenylphenol acetate* has a melting point of 63–64° after crystallization from ligroin.

Anal. Calc'd for $C_{14}H_{12}O_2$: C, 79.2; H, 5.7.

Found. C, 79.5; H, 5.6.

SUMMARY

The preparation and properties of 2,3-dihydroxybiphenyl are described. 4-Phenylcatechol and its diacetate have been obtained in a pure condition.

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY, RADIUM INSTITUTE, UNIVERSITY OF PARIS]

CARCINOGENIC DERIVATIVES OF CARBAZOLE. II. ISOSTERIC COMPOUNDS OF CARBAZOLE CONTAINING A THIOPHENE NUCLEUS[1]

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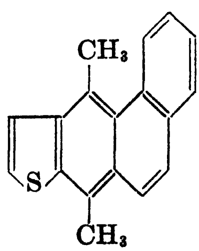
In recent years, a trend of research in chemical carcinogenesis which has proved fruitful has been the preparation and biological study of compounds derved from the basic carcinogenic hydrocarbons by replacement of a benzene nucleus with a heterocyclic one, mostly those of the pyridine and thiophene series.

In 1939, Sempronj and Morelli (1) reported the activity of β-anthraquinoline (an isolog of 1,2-benzanthracene) in the production of carcinoma of the kidney, and Joseph (2) found both 3,4-benzo-8-azaphenanthrene and pyrenoline (an isolog of the potent 3,4-benzopyrene) to be inactive. Fieser and Hershberg (3) synthesized 20-methyl-4-azacholanthrene, an isolog of the important 20-methylcholanthrene, along with other similar compounds. In 1946, Lacassagne, Buu-Hoï, Lecocq, and Rudali (4) discovered a large number of powerful carcinogens among *meso*-substituted benzacridines. In the category of substances bearing a thiophene nucleus, compounds endowed with a high degree of carcinogenicity have also been found. This was the case for 4,9-dimethyl-5,6-benzothiophanthrene (I)



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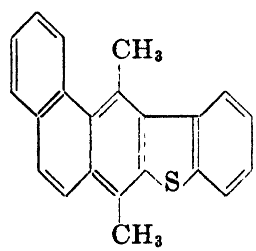


II

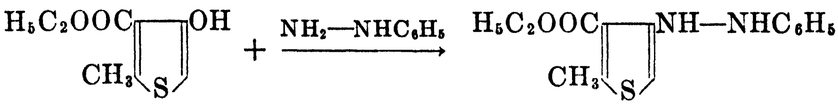
described by Fieser and Sandin (5), and of 4,9-dimethyl-2,3,5,6-dibenzothiophanthrene (II) prepared by Tilak (6). 2-Methyl-5,6-benzothiophanthrene and 2-methyl-7,8-benzothiophanthrene recently synthesized by Buu-Hoï and Hoan (7) are still under biological examination by Professor A. Lacassagne.

In this paper, we report the preparation of a number of isosteric compounds of carbazole, angular benzocarbazoles, and bisangular dibenzocarbazoles which contain a thiophene nucleus in the place of a benzene one. Two lines of synthesis have simultaneously been pursued:

(a) According to Benary and Baravian (8), 3-hydroxy-4-carbethoxy-5-methylthiophene (III), readily obtainable from ethyl acetoacetate by means of a three-step synthesis, reacts with phenylhydrazine in acetic acid medium in such a

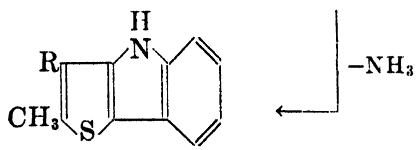
[1] The work described in this paper was carried out with the financial support of the U. S. Public Health Service, Federal Security Agency.

way that the transient 3-phenylhydrazido-4-carbethoxy-5-methylthiophene (IV) formed undergoes immediately a Fischer indole ring-closure into 3′,2′:2,3-(4′-carbethoxy-5′-methylthiopheno)indole (Va); the alkaline saponification of the

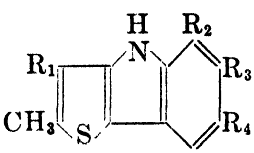


III IV

Va; $R = CO_2C_2H_5$
Vb; $R = CO_2H$
Vc; $R = H$



latter gives 3′,2′: 2,3-(4′-carboxy-5′-methylthiopheno)indole (Vb), which can be readily decarboxylated into 3′,2′:2,3-(5′-methylthiopheno)indole (Vc). We found that the same sequence of reactions could be performed with a series of diversely substituted arylhydrazines, of which the following were successfully employed: *o*-, *m*-, and *p*-tolylhydrazine, *vic.-o*-xylylhydrazine, *p*-chloro- and *p*-bromophenylhydrazine, and *p*-xenylhydrazine. The different compounds thus obtained are listed below:



VIa; $R_1 = CO_2C_2H_5, R_2 = CH_3, R_3 = R_4 = H$
VIb; $R_1 = CO_2H, R_2 = CH_3, R_3 = R_4 = H$
VIc; $R_1 = R_3 = R_4 = H, R_2 = CH_3$.

VIIa; $R_1 = CO_2C_2H_5, R_2 = R_4 = H, R_3 = CH_3$
VIIb; $R_1 = CO_2H, R_2 = R_4 = H, R_3 = CH_3$
VIIc; $R_1 = R_2 = R_4 = H, R_3 = CH_3$.

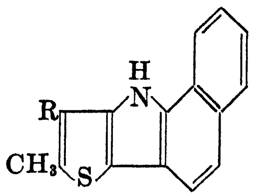
VIIIa; $R_1 = CO_2C_2H_5, R_2 = R_3 = H, R_4 = CH_3$
VIIIb; $R_1 = CO_2H, R_2 = R_3 = H, R_4 = CH_3$
VIIIc; $R_1 = R_2 = R_3 = H, R_4 = CH_3$

IXa; $R_1 = CO_2C_2H_5, R_2 = R_3 = CH_3, R_4 = H$
IXb; $R_1 = CO_2H, R_2 = R_3 = CH_3, R_4 = H$
IXc; $R_1 = R_4 = H, R_2 = R_3 = CH_3$.

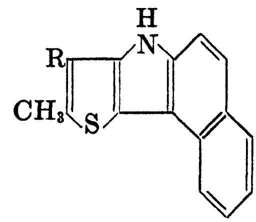
Xa; $R_1 = CO_2C_2H_5, R_2 = R_3 = H, R_4 = Cl$
Xb; $R_1 = CO_2H, R_2 = R_3 = H, R_4 = Cl$
Xc; $R_1 = R_2 = R_3 = H, R_4 = Cl$.

XIa; $R_1 = CO_2C_2H_5, R_2 = R_3 = H, R_4 = Br$.

XIIa; $R_1 = CO_2C_2H_5, R_2 = R_3 = H, R_4 = C_6H_5$.
XIIb; $R_1 = CO_2H, R_2 = R_3 = H, R_4 = C_6H_5$
XIIc; $R_1 = R_2 = R_3 = H, R_4 = C_6H_5$



XIIIa; R = $CO_2C_2H_5$
XIIIb; R = CO_2H
XIIIc; R = H.

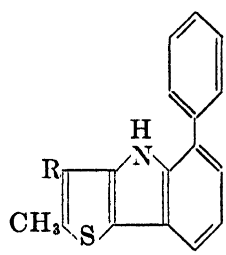


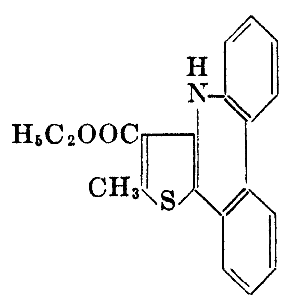
XIVa; R = $CO_2C_2H_5$
XIVb; R = CO_2H
XIVc; R = H

5-Bromo-3′,2′:2,3-(4′-carboxy-5′ -methylthiopheno)indole (XIa) was also obtained by direct treatment of (Va) with the calculated amount of bromine.

By means of α- and β-naphthylhydrazine, the synthesis of 3′,2′:2,3-(5′-methylthiopheno)-6,7-benzoindole (XIII)c and of the isomeric 3′,2′:2,3-(5′-methylthiopheno)-4,5-benzoindole (XIVc) was similarly achieved. The two latter compounds are isosteres of 6-methyl-1,2-benzocarbazole and of 6-methyl-3,4-benzocarbazole respectively, which are now under biological testing for potential carcinogenic properties. Special mention should be made of *o*-xyenylhydrazine, which gave with 3-hydroxy-4-carbethoxy-5-methylthiophene, an indole to which either formula (XVa) or (XVI) could be assigned. In view of the outstanding ease of formation of nitrogen-containing five-membered rings, we give preference to the formula (XVa) over the heptagonal one, which involves cyclisation on both phenyl nuclei.

XVa; R = $CO_2C_2H_5$
XVb; R = CO_2H
XVc; R = H



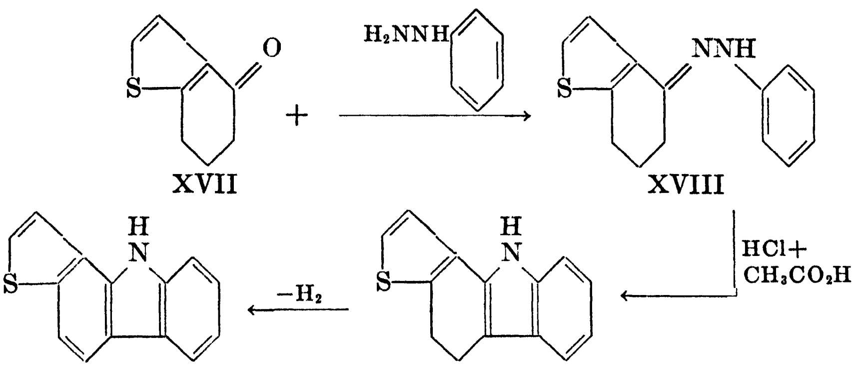


XVI

All the substances mentioned above are well-crystallised solids, giving deep halochromic coloration with sulfuric acid and dark colored picrates, as in the carbazole series. 3′,2′:2,3-(5′-Methylthiopheno)indole gave with ethylmagnesium bromide an organometallic compound, which yielded on treatment with dimethyl or diethyl sulfate oily substances believed to be 1-methyl- and 1-ethyl-3′,2′:2,3-(5′-methylthiopheno)indole respectively.

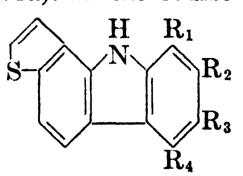
(b) A route towards thiophenocarbazoles which we have devised is the Fischer-Borsche indole ring-closure of various 4-keto-4,5,6,7-tetrahydrothianaphthene arylhydrazones, followed by dehydrogenation of the dihydro intermediates obtained. Thus, 4-keto-4,5,6,7-tetrahydrothianaphthene phenylhydrazone (XVIII) was converted by means of a solution of dry hydrogen chloride in pure

acetic acid into 3,4-dihydro-3′,2′:1,2-thiophenocarbazole (XIX) and this readily gave 3′,2′:1,2-thiophenocarbazole (XX) by heating with chloranil, a reagent previously used with success by Barclay and Campbell (9) for the dehydrogenation of tetrahydrocarbazoles, and more recently by Buu-Hoï, Hoan, and Khôi (10) for the synthesis of various dibenzocarbazoles.



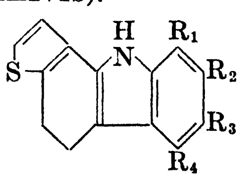
XVII XVIII XX XIX

The replacing of phenylhydrazine in the above synthesis by *o*-, *m*-, and *p*-tolylhydrazine, *vic.*-*o*- and *p*-xylylhydrazine, and *p*-xenylhydrazine, gave rise to 8-methyl- (XXIa), 7-methyl- (XXIIa), 6-methyl- (XXIIIa), 7,8-dimethyl- (XXIVa), 5,8-dimethyl- (XXV), and 6-phenyl-3′,2′:1,2-thiophenocarbazole (XXVIa). In the course of these syntheses, the following dihydro compounds



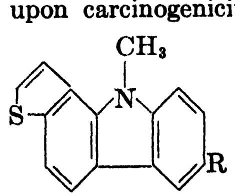
XXI a; $R_1 = CH_3$, $R_2 = R_3 = R_4 = H$
XXII a; $R_1 = R_3 = R_4 = H$, $R_2 = CH_3$
XXIIIa; $R_1 = R_2 = R_4 = H$, $R_3 = CH_3$
XXIV a; $R_1 = R_2 = CH_3$, $R_3 = R_4 = H$.
XXV ; $R_1 = R_4 = CH_3$, $R_2 = R_3 = H$.
XXVI a; $R_1 = R_2 = R_4 = H$, $R_3 = C_6H_5$.

were isolated: 8-methyl- (XXIb), 7-methyl- (XXIIb), 6-methyl- (XXIIIb), 7,8-dimethyl- (XXIVb), and 6-phenyl-3,4-dihydro-3′,2′-1,2-thiophenocarbazole (XXVIb).



XXI b; $R_1 = CH_3$, $R_2 = R_3 = R_4 = H$
XXII b; $R_1 = R_3 = R_4 = H$, $R_2 = CH_3$
XXIIIb; $R_1 = R_2 = R_4 = H$, $R_3 = CH_3$
XXIV b; $R_1 = R_2 = CH_3$, $R_3 = R_4 = H$
XXVI b; $R_1 = R_2 = R_4 = H$, $R_3 = C_6H_5$.

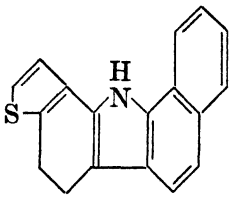
In view of the slight activity by Lacassagne, Buu-Hoï, and Zajdela (11) for 9-methyl-1,2-benzocarbazole, and of the generally enhancing influences of *meso*-substitution upon carcinogenicity (*viz.*, the cases of 9,10-dimethyl-1,2-



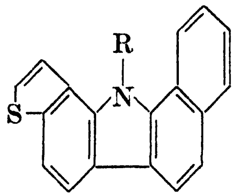
XXVII ; R = H
XXVIII; R = CH_3.

benzanthracene and of the carcinogenic benzacridines), we prepared 9-methyl- (XXVII) and 6,9-dimethyl-3′2′:1,2-thiophenocarbazole (XXVIII) by treatment with dimethyl sulphate of 3′,2′:1,2-thiophenocarbazylmagnesium bromide and 6-methyl-3′,2′:1,2-thiophenocarbazylmagnesium bromide respectively.

The Fischer-Borsche indole synthesis, applied to 4-keto-4,5,6,7-tetrahydrothianaphthene and α-naphthylhydrazine, yielded 3,4-dihydro-3′,2′:1,2-thiopheno-7,8-benzocarbazole (XXIX), which was dehydrogenated by chloranil to 3′,2′:1,2-thiopheno-7,8-benzocarbazole (XXXa); successive treatment of the latter with ethylmagnesium bromide and dimethyl sulfate yielded the correspond-

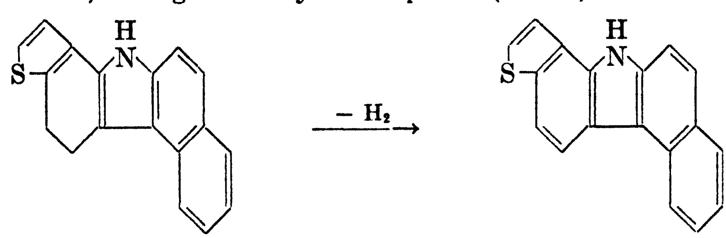


XXIX



XXXa; R = H
XXXb; R = CH_3

ing N-methyl derivative (XXXb). The same sequence of reactions performed with β-naphthylhydrazine, resulted in 3′,2′:1,2-thiopheno-5,6-benzocarbazole (XXXII) through the dihydro-compound (XXXI).



XXXI XXXII

It should be mentioned that the 4-keto-4,5,6,7-tetrahydrothianaphthene used throughout this research was prepared by cyclization of γ-2-thienylbutyryl chloride according to the excellent procedure of Fieser and Kennelly (12). These authors prepared γ-2-thienylbutyric acid (XXXIV) by means of the Clemmensen reduction of β-2-thenoylpropionic acid (XXXIII) at low temperature; we have found now that a much more convenient method for the preparation of (XXXIV)

XXXIII XXXIV

is the application to the ketoacid (XXXIII) of Huang-Minlon's modification of the Wolff-Kishner reaction (13), using hydrazine hydrate and diethylene glycol.

The various new compounds mentioned above are under biological testing by Professor Lacassagne. It may be recalled that the isosteres of (XXXa) and (XXXII), 1,2,7,8- and 1,2,5,6-dibenzocarbazole, are carcinogenic substances

with interesting peculiarities in their action, as for instance the production of remote tumors in the liver (14).

Acknowledgment. Our thanks are due to Miss P. F. Boshell, M. A. (Oxon.) for helpful assistance in this work.

EXPERIMENTAL[2]

Preparation of intermediates. The various *arylhydrazines* used in these experiments were prepared in the form of their hydrochlorides by reduction of the appropriate aryldiazonium chlorides with stannous chloride.

3-Hydroxy-4-carbethoxy-5-methylthiopthene (III). The Benary-Baravian procedure for the preparation of this compound (8) was followed except in the first step, the synthesis of ethyl β-aminocrotonate being carried out as follows: a stream of dry ammonia was bubbled for three hours into a solution of 130 g. of ethyl acetoacetate in 150 ml. of anhydrous benzene, cooled to around 4°. The half-solid mixture was kept overnight and about 100 ml. of liquid ammonia was stirred into it. After the usual treatment, over 110 g. of ethyl β-aminocrotonate was obtained.

γ-2-Thienylbutyric acid (XXXIV). β-2-Thenoylpropionic acid (40 g.) [prepared from thiophene, succinic anhydride, and aluminum chloride, according to Fieser and Kennelly (12)] was added cautiously to a solution of 40 g. of potassium hydroxide in 30 ml. of 50% hydrazine hydrate and 250 ml. of diethylene glycol. The mixture was boiled for one hour and a half for water removal, the temperature rising progressively up to 195°. The refluxing was then continued for five more hours, and the diethylene glycol distilled off under low pressure. The residue was dissolved in water, and the clear solution obtained was acidified with hydrochloric acid. The oily precipitate was taken up in ether, the ether solution dried over calcium chloride and filtered. After removal of the solvent, the residue was vacuum-distilled. γ-2-Thienylbutyric acid, b.p. 170–172°/14 mm. was thus obtained rapidly (yield: 25 g.).

7-Methyl-3′,2′:2,3-(4′-carboethoxy-5′-methylthiopheno)indole (VIa) and derivatives. A mixture of 10 g. of the ester (III), 15.5 g. of *o*-tolylhydrazine hydrochloride, 9 g. of sodium acetate, 75 ml. of acetic acid, and 25 ml. of water was refluxed three hours. After cooling and dilution with water, the precipitate obtained was recrystallized twice from benzene (charcoal), giving fine yellowish needles, m.p. 136°. The low yield obtained (30%) was probably due to the steric hindrance exerted by the *o*-methyl radical.

Anal. Calc'd for $C_{15}H_{15}NO_2S$: N, 5.1. Found: N, 5.2.

7-Methyl-3′,2′:2,3-(4′-carboxy-5′-methylthiopheno)indole (VIb) was obtained from the foregoing ester by saponification with potassium hydroxide in ethanol. It formed from chlorobenzene a colorless microcrystalline powder, m.p. 262° (decomp.).

Anal. Calc'd for $C_{13}H_{11}NO_2S$: N, 5.9. Found: N, 5.7.

Dry vacuum-distillation of a mixture of equal quantities of the foregoing acid and of calcium hydroxide yielded *7-methyl-3′,2′:2,3-(5′-methylthiopheno)indole* (VIc), which crystallized from petroleum ether in fine yellowish prisms, m.p. 110°, giving a deep brown-red coloration with pure sulfuric acid.

Anal. Calc'd for $C_{12}H_{11}NS$: N, 6.9. Found: N, 7.0.

The *picrate* thereof crystallized from benzene in fine brown-violet needles, m.p. 152°. The N-alkylation of (VIc) was performed as follows: 0.9 g. of that compound was added to a solution of ethylmagnesium bromide made from 0.24 g. of magnesium and 1.5 g. of ethyl bromide in 20 ml. of anhydrous ether. The compound dissolved with evolution of ethane; the mixture was refluxed for ten minutes, then cooled, and 1.3 g. of dimethyl sulfate was added. After ten minutes of further heating, the mixture was poured into cooled, dilute sulfuric acid, the reaction-product taken up in benzene, the benzene layer washed with an aqueous solution of sodium hydroxide and then with water, the solvent removed,

[2] All melting points are uncorrected, and were taken with a Maquenne-block.

and the residue vacuum-distilled. *1,7-Dimethyl-3',2':2,3-(5'-methylthiopheno)indole* was thus obtained as a yellow viscous oil, b.p. 235–240°/12 mm.

Anal. Calc'd for $C_{13}H_{13}NS$: N, 6.5. Found: N, 6.9.

1-Ethyl-7-methyl-3',2':2,3-(5'-methylthiopheno)indole was similarly obtained by means of diethyl sulfate (1.5 g.) in the form of a yellow oil, b.p. 235–245°/12 mm.

6-Methyl-3',2':2,3-(4'-carbethoxy-5'-methylthiopheno)indole (VIIa) and derivatives. The condensation of (III) (10 g.) with *m*-tolylhydrazine hydrochloride (15.5 g.), performed in the usual way, gave an almost quantitative yield of the *ester* (VIIa), crystallizing from benzene in fine yellowish needles, m.p. 134°.

Anal. Calc'd for $C_{13}H_{11}NO_2S$: N, 5.1. Found: N, 5.0.

6-Methyl-3',2':2,3-(4'-carboxy-5'-methylthiopheno)indole (VIIb) formed fine colorless prisms from acetic acid, m.p. 285° (decomp.).

Anal. Calc'd for $C_{13}H_{11}NO_2S$: N, 5.9. Found: N, 5.6.

6-Methyl-3',2':2,3-(5'-methylthiopheno)indole (VIIc) formed long glinting needles from ethanol, m.p. 188°; the *picrate* crystallized from benzene in silky brown-violet prisms m.p. 173°.

Anal. Calc'd for $C_{12}H_{11}NS$: N, 6.9. Found: N, 6.8.

5-Methyl-3',2':2,3-(4'-carbethoxy-5'-methylthiopheno)indole (VIIIa) and derivatives. The *ester* (yield: 98%) formed microscopic needles, m.p. 170°, from ethanol.

Anal. Calc'd for $C_{15}H_{15}NO_2S$: N, 5.2. Found: N, 5.2.

The *free acid* (VIIIb) crystallized from ethanol in colorless needles, m.p. 302° (decomp.)

Anal. Calc'd for $C_{13}H_{11}NO_2S$: N, 5.8. Found: N, 5.7.

5-Methyl-3',2':2,3-(5'-methylthiopheno)indole (VIIIc) crystallized from ethanol in fine yellowish needles m.p. 156°, giving the usual deep brown-red coloration with sulfuric acid; its *picrate* formed fine brown-violet needles, m.p. 180°.

Anal. Calc'd for $C_{12}H_{11}NS$: N, 6.6. Found: N, 6.8.

6,7-Dimethyl-3',2':2,3-(4'-carbethoxy-5'-methylthiopheno)indole (IXa) and derivatives. A low yield (*circa* 50%) of the *ester* (IXa) was obtained (steric hindrance). Yellowish needles, m.p. 142° from chlorobenzene.

Anal. Calc'd for $C_{16}H_{17}NO_2S$: N, 4.9. Found: N, 5.1.

The *free acid* (IXb) crystallized from benzene in tiny colorless needles, m.p. 250°.

Anal. Calc'd for $C_{14}H_{13}NO_2S$: N, 5.3. Found: N, 5.4.

6,7-Dimethyl-3',2':2,3-(5'-methylthiopheno)indole (IXc) formed fine brilliant yellowish needles, m.p. 165° from benzene; its *picrate* formed silky brown-violet needles, m.p. 145°.

Anal. Calc'd for $C_{13}H_{13}NS$: N, 6.5. Found: N, 6.6.

5-Chloro-3',2':2,3-(4'-carbethoxy-5'-methylthiopheno)indole (Xa) and derivatives. The condensation of (III) (3.7 g.) with *p*-chlorophenylhydrazine hydrochloride (5.5 g.), performed in the usual way, gave an almost quantitative yield of the *ester* (Xa); this formed silky colorless leaflets, m.p. 208° from chlorobenzene.

Anal. Calc'd for $C_{14}H_{12}ClNO_2S$: N, 4.8 Found: N, 5.0.

The *free acid* (Xb) crystallized from chlorobenzene in fine colorless prisms, m.p. 325° (decomp.).

Anal. Calc'd for $C_{12}H_8ClNO_2S$: N, 5.2. Found: N, 5.0.

5-Chloro-3',2':2,3-(5'-methylthiopheno)indole (Xc) was obtained by vacuum-heating the foregoing acid alone; it crystallized from ethanol in fine colorless needles m.p. 162°, giving the usual coloration with pure sulfuric acid. The corresponding *picrate* formed brown-red silky needles, m.p. 152° from benzene.

Anal. Calc'd for $C_{11}H_8ClNS$: N, 6.3. Found: N, 6.4.

5-Bromo-3',2':2,3-(4'-carbethoxy-5'-methylthiopheno)indole (XIa). (a) An ice-cooled solution of 1.28 g. of the ester (Va) in 20 ml. of acetic acid was treated with 0.8 g. of bromine dissolved in 10 ml. of acetic acid; after ten minutes, the mixture was poured on to ice, the precipitate collected, and recrystallized from ethanol. Fine colorless silky needles, m.p. 215° were thus obtained (yield 1.5 g).

(b) An almost quantitative yield of the same substance was obtained in the condensa-

tion of (III) (3 g.) with *p*-bromophenylhydrazine hydrochloride (5.5 g.) following the usual procedure. The bromination of (Va) by means of N-bromosuccinimide did not lead to the same product. This point is being further investigated.

Anal. Calc'd for $C_{14}H_{12}BrNO_2S$: N, 4.1. Found: N, 4.2.

5-Phenyl-3′,2′:2,3-(4′-carbethoxy-5′-methylthiopheno)indole (XIIa) and derivatives. The condensation of (III) (10 g.) with *p*-xenylhydrazine hydrochloride (15 g.) and sodium acetate (9 g.) in 75% acetic acid (100 ml.) gave a quantitative yield of (XIIa); this crystallized from acetic acid or chlorobenzene in silky colorless needles, m.p. 172°.

Anal. Calc'd for $C_{20}H_{17}NO_2S$: N, 4.2. Found: N, 4.2.

The *free acid* (XIIb) formed a colorless microcrystalline powder, m.p. 266° from chlorobenzene.

Anal. Calc'd for $C_{18}H_{13}NO_2S$: N, 4.5. Found: N, 4.2.

5-Phenyl-3′,2′:2,3-(5′-methylthiopheno)indole (XIIc) formed colorless needles, m.p. 160° from ligroin or ethanol, giving a greenish-brown coloration with sulfuric acid.

Anal. Calc'd for $C_{17}H_{13}NS$: N, 5.3. Found: N, 5.4.

Condensation of (III) with o-hydrazinodiphenyl. The ester (III) (10 g.) was heated with *o*-hydrazinodiphenyl hydrochloride (15 g.) in 75% acetic acid (100 ml.) in the presence of sodium acetate (9 g.).

7-Phenyl-3′,2′:2,3-(4′-carbethoxy-5′-methylthiopheno)indole (XVa ?) (15 g.), crystallized from chlorobenzene in colorless glinting needless, m.p. 124°.

Anal Calc'd for $C_{20}H_{17}NO_2S$: N, 4.2. Found: N, 4.3.

The *free acid* (XVb ?) formed colorless light leaflets, m.p. 310° (decomp.) from chlorobenzene.

Anal. Calc'd for $C_{18}H_{13}NO_2S$: N, 4.5. Found: N, 4.3.

7-Phenyl-3′,2′:2,3-(5′-methylthiopheno)indole (XVc ?) crystallized from ethanol in fine glinting colorless needles, m.p. 156°, giving with sulfuric acid a bluish coloration which rapidly became brown-red. The *picrate* is red.

Anal. Calc'd for $C_{17}H_{13}NS$: N, 5.3. Found: N, 5.2.

3′,2′:2,3-(4′-Carbethoxy-5′-methylthiopheno)-6,7-benzoindole (XIIIa) and derivatives. The thiophene (III) (9 g.) condensed with 15 g. of α-naphthylhydrazine hydrochloride in 100 ml. of 75% acetic acid in the presence of 8.5 g. of sodium acetate, gave the *ester* (XIIIa) in 90% yield. Fine colorless needles, m.p. 142°, from methanol.

Anal. Calc'd for $C_{18}H_{15}NO_2S$: N, 4.5. Found: N, 4.5.

The corresponding *acid* formed needles, m.p. 320° from ethanol.

Anal. Calc'd for $C_{16}H_{11}NO_2S$: N, 5.0. Found: N, 5.1.

3′,2′:2,3-(5′-Methylthiopheno)-6,7-benzoindole (XIIIc) crystallized from chlorobenzene in glinting colorless prisms, m.p. 165°, giving with sulfuric acid a violet coloration which rapidly turned brown-red. The *picrate* formed violet needles, m.p. 184° from benzene.

Anal. Calc'd for $C_{15}H_{11}NS$: N, 5.9. Found: N, 6.0.

3′,2′:2,3-(4′-Carbethoxy-5′-methylthiopheno)-4,5-benzoindole (XIVa) and derivatives. The condensation of (III) with β-naphthylhydrazine hydrochloride, performed as in the foregoing example, gave an equally good yield of the *ester* (XIVa), crystallizing from benzene in silky colorless needles, m.p. 209°.

Anal Calc'd for $C_{18}H_{15}NO_2S$: N, 4.5. Found: N, 4.6.

The *free acid* formed fine violet-tinged needles, m.p. 318° from chlorobenzene.

Anal. Calc'd for $C_{16}H_{11}NO_2S$: N, 5.0. Found: N, 4.9.

3′,2′:2,3-(5′-Methylthiopheno)-4,5-benzoindole (XIVc) formed silky colorless prisms, m.p. 152° from chlorobenzene, giving a deep brown-red coloration with sulfuric acid. The *picrate* crystallized from benzene in fine violet prisms, m.p. 175°.

Anal. Calc'd for $C_{15}H_{11}NS$: N, 5.9. Found: N, 6.2.

3,4-Dihydro-3′,2′:1,2-thiophenocarbazole (XIX). A solution of 1.5 g. of the ketone (XVII) and 2 g. of phenylhydrazine in 25 ml. of ethanol was refluxed for thirty minutes; the cooled mixture was poured into water, the crude phenylhydrazone (XVIII) washed with water, and vacuum-distilled; it was then refluxed for five minutes with 10 ml. of a saturated solu-

tion of hydrochloric acid in water, the solid obtained collected, washed with water, and recrystallized from benzene. Fine colorless prisms (yield: 1.5 g.), m.p. 183°, giving an orange-yellow coloration with sulfuric acid, and a dark violet molecular compound with *picric acid.*

Anal. Calc'd for $C_{14}H_{11}NS$: N, 6.2. Found: N, 6.3.

3′,2′:1,2-Thiophenocarbazole (XX). A mixture of the foregoing compound (1 g.), chloranil (1.2 g.), and dry xylene (50 ml.) was heated at 120° for three hours; the solution obtained was washed with dilute aqueous caustic soda, then with water, and dried over calcium chloride. The solvent was removed *in vacuo*, and the solid residue recrystallized twice from benzene; glinting colorless needles, m.p. 237°, giving with *picric acid* a dark violet molecular compound, and with sulfuric acid a yellow coloration which rapidly changed into blue.

Anal. Calc'd for $C_{14}H_{9}NS$: N, 6.2. Found: N, 6.2.

9-Methyl-3′,2′:1,2-thiophenocarbazole (XXVII). To a solution in ether of a Grignard reagent made from 0.3 g. of ethyl bromide and 0.1 g. of magnesium was added 0.2 g. of (XX) (evolution of ethane ensued); the mixture was refluxed for thirty minutes, then cooled, and 0.1 g. of dimethyl sulfate added. After further refluxing for thirty minutes, the reaction product was decomposed with cold, dilute sulfuric acid, the solid formed collected, washed with water, and recrystallized from benzene. Fine colorless needles, m.p. 196°, giving with sulfuric acid a yellow coloration which rapidly changed into green. The *picrate* is dark violet.

Anal. Calc'd for $C_{15}H_{11}NS$: N, 5.9. Found: N, 6.1.

8-Methyl-3,4-dihydro-3′,2′:1,2-thiophenocarbazole (XXIb). The *o*-tolylhydrazone of the ketone (XVII) was prepared by refluxing for an hour a mixture of 1.2 g. of (XVII), 2.4 g. of *o*-tolylhydrazine hydrochloride, and 3 g. of sodium acetate in 30 ml. of ethanol. The indolization was performed in the usual way; (XXIb) crystallized from ligroin in yellowish prisms, m.p. 163°, very soluble in benzene, and giving with sulfuric acid a yellow coloration which turned blue; yield: 0.6 g. The *picrate* is violet.

Anal. Calc'd for $C_{15}H_{13}NS$: N, 5.8. Found: N, 5.8.

8-Methyl-3′,2′:1,2-thiophenocarbazole (XXIa). Crystallized from benzene in fine almost colorless prisms, m.p. 190°, giving with sulfuric acid the same coloration as above. The *picrate* formed silky, violet needles, m.p. 208°.

Anal. Calc'd for $C_{15}H_{11}NS$: N, 5.9. Found: N, 5.6.

7-Methyl-3,4-dihydro-3′,2′:1,2-thiophenocarbazole (XXIIb). Formed a colorless, microcrystalline powder, m.p. 159° from ligroin (yield: 0.9 g.). The coloration with sulfuric acid was orange-yellow, turning into blue.

Anal. Calc'd for $C_{15}H_{13}NS$: N, 5.8. Found: N, 5.5.

7-Methyl-3′,2′:1,2-thiophenocarbazole (XXIIa). Glinting, yellowish needles (from benzene), m.p. 255°, which sublimed easily above 200°.

Anal. Calc'd for $C_{15}H_{11}NS$: N, 5.9. Found: N, 5.8.

6-Methyl-3,4-dihydro-3′,2′:1,2-thiophenocarbazole (XXIIIb). Crystallized from benzene in colorless needles, m.p. 205°, giving with sulfuric acid an orange coloration which turned green, yield: 1.1 g.

Anal. Calc'd for $C_{15}H_{13}NS$: N, 5.8. Found: N, 5.6.

6-Methyl-3′,2′:1,2-thiophenocarbazole (XXIIIa). Formed fine glinting yellowish prisms, m.p. 264° from benzene.

Anal. Calc'd for $C_{15}H_{11}NS$: N, 5.9. Found: N, 5.8.

6,9-Dimethyl-3′,2′:1,2-thiophenocarbazole (XXVIII). The N-alkylation of (XXIIIa) was performed with dimethyl sulfate as in the case of (XXVII). The product crystallized from methanol in colorless needles, m.p. 173°, giving with sulfuric acid an orange coloration turning green.

Anal. Calc'd for $C_{16}H_{13}NS$: N, 5.5. Found: N, 5.4.

7,8-Dimethyl-3,4-dihydro-3′,2′:1,2-thiophenocarbazole (XXIVb). Yellowish microcrystalline powder (from ligroin), m.p. 160°, giving with sulfuric acid a yellow coloration turning green; yield: 0.8 g. from 1.2 g. of (XVII) and 2 g. of *vic.-o*-xylylhydrazine hydrochloride.

Anal. Calc'd for $C_{16}H_{15}NS$: N, 5.5. Found: N, 5.6.

7,8-Dimethyl-3′,2′:1,2-thiophenocarbazole (XXIVa). Almost colorless needles (from benzene) m.p. 206°; the *picrate* is deep violet.

Anal. Calc'd for $C_{16}H_{13}NS$; N, 5.5. Found: N, 5.6.

5,8-Dimethyl-3′,2′:1,2-thiophenocarbazole (XXV). The corresponding dihydro compound could not be isolated in a pure state, owing to its great oxidizability. The compound (XXV) crystallized from ligroin in yellowish needles, m.p. 170°, giving with sulfuric acid a yellow coloration turning green. Yield: 0.8 g. from 1.2 g. of (XVII) and 2 g. of *p*-xylylhydrazine.

Anal. Calc'd for $C_{16}H_{13}NS$: N, 5.5. Found: N, 5.4.

6-Phenyl-3,4-dihydro-3′,2′:1,2-thiophenocarbazole (XXVIb), formed yellowish needles, m.p. 166° from benzene; gave with sulfuric acid an orange coloration turning green, and with *picrate acid* a violet molecular compound; yield: 1.1 g. from 1.2 g. of (XVII) and 2.7 g. of *p*-xenylhydrazine hydrochloride.

Anal. Calc'd for $C_{20}H_{15}NS$: N, 4.6. Found: N, 4.8.

6-Phenyl-3′,2′:1,2-thiophenocarbazole (XXVIa). Glinting, colorless leaflets (from benzene), m.p. 244° (abundant sublimation above 240°); the corresponding *picrate* crystallized from benzene in silky, violet needles, m.p. 171°.

Anal. Calc'd for $C_{20}H_{13}NS$: N, 4.6. Found: N, 4.6.

3,4-Dihydro-3′,2′:1,2-thiopheno-7,8-benzocarbazole (XXIX), crystallized from benzene in fine yellowish prisms, m.p. 225°, giving with sulfuric acid a violet coloration turning into dark green; the corresponding *picrate* is deep violet; yield: 1.5 g. from 1.5 g. of (XVII), 2.8 g. of α-naphthylhydrazine hydrochloride, and 3 g. of sodium acetate.

Anal. Calc'd for $C_{18}H_{13}NS$: N, 5.0. Found: N, 5.2.

3′,2′:1,2-Thiopheno-7,8-benzocarbazole (XXXa). Glistening yellowish leaflets (from benzene), m.p. 232°, giving with sulfuric acid a deep red coloration, and with *picric acid* a dark violet, molecular compound.

Anal. Calc'd for $C_{18}H_{11}NS$: N, 5.1. Found: N, 5.1.

9-Methyl-3′,2′:1,2-thiopheno-7,8-benzocarbazole (XXXb), crystallized from methanol in fine yellowish needles, m.p. 251°, giving with sulfuric acid a dark brown-red coloration.

Anal. Calc'd for $C_{19}H_{13}NS$: N, 4.8. Found: N, 4.9.

3,4-Dihydro-3′,2′:1,2-thiopheno-5,6-benzocarbazole (XXXI), crystallized from benzene in yellowish prisms, m.p. 213–214°, giving a dark brown-red coloration with sulfuric acid; yield: 1.5 g.

Anal. Calc'd for $C_{18}H_{13}NS$: N, 5.0. Found: N, 5.2.

3′,2′:1,2-Thiopheno-5,6-benzocarbazole (XXXII), formed from benzene yellowish prisms, m.p. 223°, giving with sulfuric acid a brown-red coloration turning into dark green; the *picrate* crystallized from benzene in silky, dark violet needles, m.p. 209°.

Anal. Calc'd for $C_{18}H_{11}NS$: N, 5.1. Found: N, 5.3.

SUMMARY

1. The condensation of 3-hydroxy-4-carbethoxy-5-methylthiophene with a series of arylhydrazines has been investigated with the view of obtaining isosteric compounds of carbazole containing a thiophene nucleus.

2. The Fischer-Borsche synthesis of a number of thiophene analogs of carcinogenic mono- and di-benzocarbazoles from 4-keto-4,5,6,7-tetrahydrothianaphthene and various arylhydrazines is reported.

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ALKYLHYDRAZINES

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In the course of our work on derivatives of 5-nitro-2-furaldehyde it became desirable to prepare some 2-alkylsubstituted semicarbazides. Since, in our opinion, the most convenient method of preparing 2-alkylsemicarbazides is the treatment of the appropriate monoalkylhydrazine with cyanic acid, it was necessary to find a suitable way to prepare the required hydrazines.

Westphal (1) has shown that higher alkylsubstituted hydrazines (hexyl and above) can be prepared in good yields from hydrazine and the appropriate alkyl halide. This method, when applied to the lower alkyl halides leads chiefly to di-, tri-, and tetra-substituted hydrazines and to quaternary ammonium salts.

The lowest member of this series, methylhydrazine, can be conveniently prepared by the action of dimethyl sulfate on benzalazine (2).

The methods for preparing the intermediate hydrazines (ethyl through amyl), however, are few. Those reported are either tedious and complicated or give poor yields. The preparation of *n*-butyl- and *n*-amyl-hydrazine could not be found in the literature.

Ethylhydrazine has been prepared by Thiele and Meyer (3) in moderate yield by the reduction of ethyl nitramine with zinc and hydrochloric acid. Fischer (4) prepared this compound in good yield by reducing N-nitroso-N,N′-diethylurea with zinc and acetic acid. Zerner (5) obtained some ethylhydrazine by the reaction of ethylmagnesium iodide with diazoacetic acid and hydrolyzing with dilute sulfuric acid. Thiele (2) mentions the preparation of ethylhydrazine from ketazine and ethyl bromide, but gives no details.

Propylhydrazine has been prepared by Stolle (6) by the treatment of potassium propyl sulfate with hydrazine. Taipale and Smirnov (7) report the preparation of this compound by the hydrolysis of azopropane.

Isopropylhydrazine has been synthesized by Lochte, Noyes, and Bailey (8) by the hydrogenation with colloidal platinum of a mixture of acetone, hydrazine hydrate, and hydrochloric acid. They also prepared it by the treatment of 2,2′-azobispropane with 18% hydrochloric acid. Neighbors and co-workers (9) obtained isopropylhydrazine by treating 1-isopropylsemicarbazide with 80% sulfuric acid. Independently, Taipale (10) prepared isopropylhydrazine by treatment of 2,2′-azobispropane with alcoholic hydrogen chloride. Also, (10) he obtained it by the distillation of N-nitroso-N,N′-diisopropylhydrazine. Klages, Nober, Kircher, and Bock (11) obtained very poor yields of crude isopropylhydrazine from the treatment of hydrazine with isopropyl bromide.

Although, as stated previously, *n*-butyl- and *n*-amyl-hydrazines are not reported, Taipale and Usachev (12) prepared *sec*-butyl- and *sec*-amyl-hydrazine by the treatment of the corresponding azo compounds with sodium hydroxide.

Sommer, Schultz, and Nassau (13, 14) reported the preparation of methyl-,

benzyl-, piperidyl- and 2-aminoethyl-hydrazines as well as several arylhydrazines in good yield by the treatment of the corresponding amines with hydroxylamine-O-sulfonic acid (called HOS in subsequent references) in the presence of alkali. The only other reference reporting the application of this method is that of Berger (15), who treated 1-amino-1-phenylacetic acid with HOS to give an unreported yield of 1-phenyl-1-hydrazinoacetic acid. His attempts to prepare the hydrazino acid from 1-amino-1,1-diethylacetic acid resulted in failure.

In view of the ready availability of the necessary amines and the apparent simplicity of the method, the synthesis utilizing HOS was adopted as the most promising for the preparation of the desired alkylhydrazines. Ethyl-, propyl-, isopropyl-, *n*-butyl- and *n*-amyl-hydrazines were prepared in good yields, as was 2-hydroxyethylhydrazine.

HOS is easily prepared by the reaction of hydroxylamine sulfate with chlorosulfonic acid or oleum (13, 16). This hydrazine synthesis is relatively simple; the appropriate amine, potassium hydroxide, and water are mixed together and the HOS, in ice-water, added. The solution is heated to reflux and acidified, concentrated, and filtered from inorganic salts. The filtrate is treated with benzaldehyde, the benzalhydrazone extracted with ether and the ether solution steam-distilled from an aqueous oxalic acid solution until all benzaldehyde is removed. Upon cooling the residue the desired oxalate separates.

Sommer (13) reported a 40% yield[1] of 1-hydrazino-2-aminoethane from ethylenediamine using a ratio of amine to HOS of 1:1. In repeating this work we were able to obtain a yield of only 3%. However, by raising the ratio of amine to HOS to 3:1 and reducing the amount of water, thereby increasing the concentration of amine, yields of 27% were attained. This increased ratio of amine to HOS was successfully applied to the other alkylhydrazine preparations despite Sommer's statement that equimolar ratios were desirable. Optimum conditions were not determined but a ratio of 6–7:1 gave good yields.

Some modifications were made in Sommer's method which simplified the procedure considerably. As he suggested, the HOS solution was added dropwise to the refluxing solution of amine and potassium hydroxide. By using a smaller amount of water it was found that concentration of the reaction mixture was not necessary. It was further found that the potassium hydroxide was not necessary; instead a still larger excess of the amine was used. The yields were better than in the cases in which the inorganic base was employed.

Although HOS reacts with alcohols to give the alkyl sulfates of hydroxylamine (13), the reaction is apparently slower than that with amines. It was thought, therefore, that the treatment of ethanolamine with HOS should give 2-hydroxyethylhydrazine. This was found to be the case and the latter was prepared in good yield. Again it was found that equimolar ratios of amine to HOS gave low yields (10%). Using a ratio of 6:1 a yield of 48% was obtained. Since potassium hy-

[1] The yield is given in both percentage and weight. The weight of product reported corresponds to a yield of 80% but this figure, too, is ambiguous because the weight of benzaldehyde used to make the intermediate hydrazone would allow a maximum yield of 57%.

droxide is soluble in ethanolamine, one run was made in which no water was used (except enough to dissolve the HOS) and the ratio of amine to HOS was 12:1. A yield of 50% was obtained, indicating that there is a practical limit for the amine to HOS ratio as far as increase in yield is concerned. The possibility exists that the HOS reacted with both the hydroxyl and amino groups, and during the isolation procedure the hydrazinoalkyl sulfate hydrolyzed to give the desired hydrazinoalcohol.

All of the prepared alkylhydrazine oxalates were converted to the corresponding 5-nitro-2-furaldehyde 2-alkylsemicarbazones. Neutralized aqueous solutions of the former were treated with potassium cyanate. The semicarbazides themselves were not isolated; instead their acidified solutions were treated with alcoholic solutions of 5-nitro-2-furaldehyde, whereupon the slightly soluble yellow semicarbazones precipitated.

EXPERIMENTAL[2]

Hydroxylamine-O-sulfonic acid. The HOS was prepared, using the method of Sommer, *et al.* (13), by interaction of chlorosulfonic acid and hydroxylammonium sulfate. Commercial grade reagents were employed with satisfactory results. Yields of 90–95% of product analyzing 86–95%, by iodometric titration, were obtained. The 95% HOS was used except where otherwise indicated.

1-Hydrazino-2-aminoethane dioxalate. (a) Fifty cc. of 10% ethylenediamine (0.083 mole), and a solution of 9.3 g. of potassium hydroxide in 200 cc. of water were mixed. A solution of 9.8 g. (0.083 mole) of HOS in 20 cc. of ice-water was added and the solution heated to reflux in seven minutes and held there for fifteen minutes. Ten cc. of glacial acetic acid was added and 90 cc. of distillate removed at atmospheric pressure. Distillation was continued at reduced pressure (90 mm.) until 110 cc. of liquid residue remained. The latter was cooled in an ice-bath, following which the crystals of inorganic salt were filtered off. The filtrate was warmed to 50°, 5 g. (0.047 mole) of benzaldehyde added and the emulsion stirred at 50° for five minutes. It was then cooled and extracted with two 50-cc. and one 25-cc. portions of ether. The ether extracts were added to a solution of 7.5 g. of anhydrous oxalic acid in 100 cc. of water, plus Darco, and the mixture steam-distilled until no more benzaldehyde came over. Upon filtering the 250 cc. of residue and cooling, a white solid separated. Yield 0.6 g., (3%), m.p. 180–185°.[3] Concentration of the filtrate yielded only oxalic acid.

(b) Fifteen grams (0.25 mole) of ethylenediamine, 135 cc. of water, and 9.4 g. of potassium hydroxide were mixed and heated to reflux. Over a period of twenty minutes a solution of 9.9 g. (0.083 mole) of HOS in 25 cc. of ice-water was added with mechanical stirring. Refluxing was continued for one-half hour, the solution cooled and then acidified with 20 cc. of glacial acetic acid. The solution was concentrated to 100 cc. at atmospheric pressure, cooled, the inorganic salts filtered off and the filtrate condensed with 9 g. (0.085 mole) of benzaldehyde. It was extracted with three 50-cc. portions of ether and the ether extract added to a solution of 15 g. of oxalic acid dihydrate, plus Darco, in 100 cc. of water. Steam-distillation was carried out until no more benzaldehyde came over. Upon filtering the 200 cc. of residue and cooling, 5.6 g., (27%), of *1-hydrazino-2-aminoethane dioxalate* were obtained, m.p. 193–195°. Recrystallization from 25% alcohol gave a melting point of 206°.

Anal. Calc'd for $C_6H_{13}N_3O_8$: C, 28.24; H, 5.14.

Found: C, 28.13; H, 5.20.

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[2] All melting points were taken on the Fisher-Johns apparatus. Microanalyses, solubilities, and ultraviolet absorbtion curves were done by Mr. A. Caprio.

[3] Sommer, *et al.* (13), report 204°.

n-Amylhydrazine oxalate. One hundred fifty cc. of water, 47.5 g. (0.55 mole) of *n*-amylamine, and 9.4 g. of potassium hydroxide were mixed, two layers forming. The mixture was heated to reflux with stirring and a solution of 9.9 g. (0.083 mole) of HOS in 50 cc. of ice water was added dropwise over a period of one half hour. The solution was then cooled, acidified with 70 cc. of glacial acetic acid and 50 cc. of distillate removed at atmospheric pressure. The residue was cooled and the inorganic salts filtered off. The filtrate was warmed to 50° and stirred with 9 g. of benzaldehyde for ten minutes. The emulsion was cooled and extracted with three 50-cc. portions of ether. The ether extracts were added to a solution of 20 g. of oxalic acid dihydrate in 100 cc. of water, Darco added, and the mixture steam-distilled until no more benzaldehyde distilled over. Upon filtering and cooling, a white solid separated. The precipitate was filtered off and the filtrate was concentrated to 20 cc., whereupon more solid separated. The two solids were combined and recrystallized from 150 cc. of SDA #30 alcohol.[4] Yield 5.0 g., (31%), m.p. 164°.

Anal. Calc'd for $C_7H_{16}N_2O_4$: C, 43.74; H, 8.39.

Found: C, 43.16; H, 8.45.

n-Butylhydrazine oxalate. The same procedure used in the preparation of *n*-amylhydrazine oxalate was applied to *n*-butylamine, using 120 cc. of water, 37 g. (0.51 mole) of *n*-butylamine, 11 g. of potassium hydroxide, and 9.9 g. (0.083 mole) of HOS in 25 cc. of water. Yield 6.7 g., (45%), m.p. 165°.

Anal. Calc'd for $C_6H_{14}N_2O_4$: C, 40.44; H, 7.92.

Found: C, 40.00; H, 7.99.

n-Propylhydrazine oxalate. The same procedure was applied to *n*-propylamine using 100 cc. of water, 25.0 g. (0.42 mole) of *n*-propylamine, 9.9 g. of potassium hydroxide, and a solution of 8.5 g. (0.072 mole) of HOS in 20 cc. of water. Yield 6.1 g., (52%), m.p. 175°.

Anal. Calc'd for $C_5H_{12}N_2O_4$: C, 36.58; H, 7.37.

Found: C, 36.36; H, 7.91.

Isopropylhydrazine oxalate. The same procedure was applied to isopropylamine using 125 cc. of water, 36 g. (0.61 mole) of isopropylamine, 11 g. of potassium hydroxide, and a solution of 9.9 g. (0.083 mole) of HOS in 20 cc. of water. Yield 6.0 g., (44%), m.p. 172°. Taipale (10) reports the melting point 156°.

Anal. Calc'd for $C_5H_{12}N_2O_4$: C, 36.58; H, 7.37.

Found: C, 36.48; H, 7.55.

Ethylhydrazine oxalate. Forty grams (0.49 mole) of ethylamine hydrochloride was dissolved in 50 cc. of water and cooled in an ice-bath. A solution of 51 g. of potassium hydroxide in 50 cc. of water was cautiously added so that the temperature remained below 15°. The solution was then heated to reflux and with mechanical stirring a solution of 9.9 g. (0.083 mole) of HOS in 25 cc. of water added over a period of ten minutes. The solution was cooled and neutralized with 50 cc. of glacial acetic acid. The precipitated salts were filtered off and the filtrate warmed at 50° with 9 g. of benzaldehyde. The resulting emulsion was cooled, extracted with three 50-cc. portions of ether and the ether extract added to a solution of 11 g. of oxalic acid dihydrate in 50 cc. of water. The mixture was steam-distilled until no more benzaldehyde came over. The residue was evaporated to dryness *in vacuo*, and the residual solid recrystallized from 100 cc. of SDA #30 alcohol.Yield 5.2 g., (42%), m.p. 170–171°.

Anal. Calc'd for $C_4H_{10}N_2O_4$: C, 32.00; H, 6.71.

Found: C, 32.21; H, 6.77.

2-Hydroxyethylhydrazine oxalate. (a) Five grams (0.082 mole) of ethanolamine was dissolved in 25 cc. of water and a solution of 11 g. of potassium hydroxide in 35 cc. of water added. The solution was heated to 95° on the steam-bath and a solution of 10.8 g (0.082 mole) of HOS (86%) in 20 cc. of ice-water added over a period of thirteen minutes. The solution was heated at 95° for fifteen minutes, cooled and acidified with 35 cc. of glacial acetic acid. After filtering off the inorganic salts, the filtrate was warmed to 55° and stirred

[4] Denatured ethyl alcohol.

with 15 g. of benzaldehyde for ten minutes, cooled and extracted with three 50-cc. portions of ether. The ether extracts were added to a solution of 15 g. of oxalic acid dihydrate in 50 cc. of water and the mixture steam-distilled until no more benzaldehyde came over. The residue was concentrated to dryness *in vacuo* and the solid recrystallized from SDA #30 alcohol. Yield 1.3 g., (10%), m.p. 106°.

(b) Using exactly the same conditions and reagents, except that the amount of ethanolamine was raised to 31 g. (0.51 mole), the yield was 6.5 g., (48%), m p. 106°.

(c) Using the same reagents and procedure, except that no water (other than that to dissolve the HOS) was used and the amount of amine was 61 g. (1.0 mole), the yield was 6.8 g. (50%), m.p. 106°.

Anal. Calc'd for $C_4H_{10}N_2O_5$: C, 28.92; H, 6.07.

Found: C, 28.78; H, 6.50.

A sample of 2-hydroxyethylhydrazine prepared by the method of Gabriel (17) was converted to the oxalate by dissolving equimolar amounts of oxalic acid and the 2-hydroxyethylhydrazine in absolute alcohol. The resulting precipitate was recrystallized from SDA #30 alcohol, m.p. 106°. A mixed melting point with the material prepared by the HOS method gave no depression.

PREPARATION OF ALKYLHYDRAZINE OXALATES WITHOUT THE USE OF INORGANIC BASE

n-Butylhydrazine oxalate. Thirty-seven grams (0.51 mole) of *n*-butylamine was mixed with 15 cc. of water and heated to reflux. With stirring, a solution of 5.0 g. (0.042 mole) of HOS in 15 cc. of water was added dropwise over a period of eight minutes. After completion of addition the solution was cooled, acidified with 30 cc. of glacial acetic acid and warmed to 50° with 9 g. of benzaldehyde for ten minutes. The resulting emulsion was cooled and extracted with three 50-cc. portions of ether. The ether extracts were added to a solution of 7 g. of oxalic acid dihydrate in 25 cc. of water and the mixture steam-distilled until no more benzaldehyde came over. The residue was concentrated to dryness *in vacuo* and the solid residue recrystallized from 100 cc. of SDA #30 alcohol. Yield 4.5 g., (60%), m.p. 165°.

Isopropylhydrazine oxalate. The same procedure was followed using 118 g. (2.0 moles) of isopropylamine, 25 cc. of water, and a solution of 20 g. (0.169 mole) of HOS in 40 cc. of water. Yield 14.3 g., (52%), m.p. 172°.

5-NITRO-2-FURALDEHYDE 2-ALKYLSEMICARBAZONES

The corresponding 5-nitro-2-furaldehyde 2-alkylsemicarbazones derived from the alkylhydrazine oxalates were prepared by identical procedures. As an example, that used to prepare the *n*-amyl derivative will be presented.

5-Nitro-2-furaldehyde 2-n-amylsemicarbazone. Two grams of *n*-amylhydrazine oxalate was dissolved in 100 cc. of water and the *p*H was adjusted to 7 with dilute sodium hydroxide. A solution of 0.85 g. of potassium cyanate in 10 cc. of water was added and the resulting solution allowed to stand overnight at room temperature. It was then acidified with dilute hydrochloric acid and a solution of 1.5 g. of 5-nitro-2-furaldehyde in 10 cc. of alcohol added, whereupon a yellow solid precipitated. This was filtered off, washed with water, and dried. Yield 1.9 g., (68%). After recrystallization from dilute alcohol, the m.p. was 127–128°. Its solubility in water at 25° was 34 mg./l. Ultraviolet absorption maxima in water were observed at 2700 Å and 3900 A, E_m = 12,300 and 16,100, respectively.

Anal. Calc'd for $C_{11}H_{16}N_4O_4$: C, 49.24; H, 6.01.

Found: C, 49.01; H, 5.83.

5-Nitro-2-furaldehyde 2-n-butylsemicarbazone. M.p. 123°, yield 37%, water solubility 117 mg./l., ultraviolet absorption maxima at 2700 Å and 3900 Å, E_m = 12,900 and 16,000, respectively.

Anal. Calc'd for $C_{10}H_{14}N_4O_4$: C, 47.24; H, 5.55.

Found: C, 47.12; H, 5.30.

5-Nitro-2-furaldehyde 2-n-propylsemicarbazone. M.p. 157–158°, yield 47%, water solubility 250 mg./l., ultraviolet absorbtion maxima at 2700 Å and 3875 Å, E_m = 13,200 and 16,600, respectively.

Anal. Calc'd for $C_9H_{12}N_4O_4$: C, 45.00; H, 5.04.

Found: C, 44.94; H, 5.15.

5-Nitro-2-furaldehyde 2-isopropylsemicarbazone. M.p. 177°, yield 33%, water solubility 230 mg./l., ultraviolet absorbtion maxima at 2700 Å and 3900 Å, E_m = 10,400 and 15,500, respectively.

Anal. Calc'd for $C_9H_{12}N_4O_4$: C, 45.00; H, 5.04.

Found: C, 45.19; H, 5.17.

5-Nitro-2-furaldehyde 2-ethylsemicarbazone. M.p. 203–204°, yield 50%, water solubility 260 mg./l., ultraviolet absorbtion maxima at 2700 Å and 3850 Å, E_m = 12,300 and 16,100, respectively.

Anal. Calc'd for $C_8H_{10}N_4O_4$: C, 42.48; H, 4.46.

Found: C, 42.74; H, 4.44.

SUMMARY

Alkylhydrazines, ethyl through amyl, have been prepared in good yield by the treatment of the corresponding amine with hydroxylamine-O-sulfonic acid.

2-Hydroxyethylhydrazine has also been prepared by this method.

The corresponding 5-nitro-2-furaldehyde 2-substituted semicarbazones have been prepared from the alkylhydrazines synthesized above.

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[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY, UNIVERSITY OF CHICAGO]

STUDIES PERTAINING TO THE MECHANISM OF THE HETEROGENEOUS CANNIZZARO REACTION[1]

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INTRODUCTION

The previous literature relating to the mechanism of the Cannizzaro reaction has been reviewed by Geissman (1) and by Alexander (2). The formulation of an adequate mechanistic hypothesis must integrate three salient facts.

1. The homogeneous reactions are characterized by third-order kinetics, the rates being representable by the equation: $d(\text{ArCHO})/dt = k(\text{ArCHO})^2(\text{OH}^-)$ (3, 4, 5, 6).

2. As demonstrated by the experiments of Fredenhagen and Bonhoeffer (7), performed in deuterated aqueous media, the hydrogen transfer involved in the Cannizzaro reaction takes place directly between aldehyde molecules, without intervention of the medium.

3. Benzyl benzoate has been isolated from benzaldehyde Cannizzaro reaction mixtures by Lachmann (8), and is therefore, under certain reaction conditions at least, an intermediate. No simple mechanistic formulation as yet proposed takes account of all three of these facts.

The present study of the heterogeneous Cannizzaro reaction, undertaken with the objectives of supplementing and, if possible, correlating the known facts, encountered special problems not ordinarily met in studies of the homogeneous reaction. The most significant of these, the elucidation of which constitutes the subject-matter of the present report, are: (a) anomalous variations in reaction rate dependent on the origin and history of the aldehyde; (b) abnormal variations in reaction rate with changing alkali concentration; (c) autocatalysis of the reaction; (d) the question of the locus of the reaction; and (e) abnormal differences in the reaction rates of substituted benzaldehydes.

To spare the reader unnecessary suspense and to facilitate his assimilation of the discussion that follows it may be stated at this point that, as conducted in this study, and as ordinarily employed preparationally, the so-called heterogeneous Cannizzaro reaction is essentially a composite of two homogeneous reactions occurring simultaneously in the two phases, the non-aqueous phase reaction being catalyzed by a product of the aqueous phase reaction.[2] Appar-

[1] The authors express their sincere appreciation to the Research Corporation for the grant which made these studies possible.

[2] There is considerable evidence to suggest that, under certain experimental conditions, there may also be a Cannizzaro dismutation of the free-radical chain-reaction type. See *e.g.*: Haber and Willstätter, *Ber.*, **69**, 2844 (1931); Kharasch and Foy, *J. Am. Chem. Soc.*, **57**, 1510 (1935); Urushibara and Takebayashi, *Bull. Chem. Soc. Japan*, **12**, 328 (1937); Weiss, *Trans. Faraday Soc.*, **37**, 782 (1941). That problem is under further investigation in this laboratory.

ently the phase interface plays no significant part in any rate-determining step of the over-all reaction.

DESCRIPTION OF THE PRESENT STUDY

Anomalous variations in reaction rate with origin and history of the aldehyde. Moderate precautions suffice to insure highly reproducible reaction rates for the homogeneous Cannizzaro reaction in dilute solutions. Moreover, despite repeated attempts, no accelerators or inhibitors for the homogeneous reaction have been found except in the special case of formaldehyde. For the heterogeneous Cannizzaro reaction, on the other hand, reproducible rates are attainable only with rigorous application of special precautions.

Earlier studies in this laboratory by Kharasch and Foy (9) and Kharasch and Chenicek (10) revealed that no two samples of aldehyde were likely to undergo reaction at the same rate, and that for a given sample the reaction rate might vary erratically with aging. It was shown that, in general, the reaction rate was increased by exposure of the aldehyde to air or light, and that the increase in rate was roughly proportional to the duration and intensity of exposure. Slow, reproducible reaction rates were eventually obtained with aldehyde samples which had been subjected to low-temperature, low-pressure distillation in the dark.

TABLE I

EFFECT OF ULTRAVIOLET ILLUMINATION OF BENZALDEHYDE ON RATE OF HETEROGENEOUS CANNIZZARO REACTION

CHARACTER OF SAMPLE	% CONVERSION (1 HR., 25°)
Purified benzaldehyde	11
Purified, irradiated benzaldehyde	88
Irradiated, redistilled benzaldehyde	14
Purified benzaldehyde with distillation residue from irradiated benzaldehyde added	82

It was shown by Kharasch and Richlin (11) that ultraviolet irradiation of degassed benzaldehyde in evacuated quartz vessels produces a relatively non-volatile accelerator (or accelerators) of the heterogeneous Cannizzaro reaction. The data of Table I, taken from unpublished work of Kharasch and Richlin (11), relating to experiments in which 5 cc. each of 48.2% aqueous potassium hydroxide and benzaldehyde were agitated in 18-cc. sealed tubes, indicate qualitatively the rate-accelerating effect of the photochemical product(s).

In experiments preliminary to the present study it was found that sunlight irradiation of benzaldehyde gives rise to a complex mixture of products which includes high-molecular-weight "polymer", benzoic acid, stilbene, benzoin, mesohydrobenzoin, mesohydrobenzoin dibenzoate, and, very probably, benzoin benzoate and benzil. Tests for accelerating properties revealed that mesohydrobenzoin significantly increases the rate of the heterogeneous reaction of benzaldehyde with 46% aqueous potassium hydroxide. Surprisingly enough

dl-hydrobenzoin was found to effect a considerably greater rate-acceleration.[3] Representative data relating to experiments conducted at room temperature are presented in Table II.

Geib's (12) suggestion that the increase in heterogeneous Cannizzaro reaction rates when primary, or, to a lesser extent when secondary, alcohols are added to the reaction system is attributable to alterations in phase relationships scarcely seems adequate in this instance. The rate-accelerating influence of the hydrobenzoins has the appearance of a catalytic effect. Accordingly, several more or less similar glycols were tested for accelerating properties. In one series of experiments phenylethylene glycol and 1-phenyl-1,3 propanediol were both

TABLE II

EFFECT OF HYDROBENZOINS ON RATE OF HETEROGENEOUS REACTION OF PURIFIED BENZALDEHYDE (5 CC.) WITH 46% AQUEOUS POTASSIUM HYDROXIDE (5 CC.)

HYDROBENZOIN	% CONVERSION (1.75 HR.)
None	3.6
Meso- (100 mg.)	23.5
Racemic (100 mg.)	41.9

TABLE III

EFFECT OF VARIOUS GLYCOLS ON RATE OF HETEROGENEOUS REACTION OF PURIFIED BENZALDEHYDE (5 CC.) WITH 40% AQUEOUS POTASSIUM HYDROXIDE (5 CC.)

GLYCOL	REACTION TIME (HRS.)	% CONVERSION
None	1.5	3.6
Phenylethylene glycol	1.5	55.0
1-Phenyl-1,3-propanediol	1.5	48.5
None	2.0	8.2
Ethylene glycol	2.0	5.8
Glycerol	2.0	7.2
Pinacol	3.0	8.2

found to be somewhat superior to the hydrobenzoins as accelerators; in another series ethylene glycol, glycerol, and pinacol were found to be ineffective. Relevant data are presented in Table III.

Analysis of the nature of the catalytic action of the glycols is deferred to a later portion of this discussion. However, two conclusions may be drawn at this point.

1. The heterogeneous reaction is subject to accelerating influences which do not affect the homogeneous reaction in more or less aqueous solutions.
2. Some members of the classes of compounds which accelerate the heterogeneous reaction are normal impurities in benzaldehyde (and probably in substituted benzaldehydes as well).

[3] *dl*-Hydrobenzoin has not been isolated from irradiated benzaldehyde but is, nonetheless, a probable photochemical reaction product.

It follows that the rate of a heterogeneous Cannizzaro reaction has no significance unless the purity of the aldehyde is rigidly controlled.

Abnormal variations in rate of the heterogeneous Cannizzaro reaction with changing alkali concentration. It is well established that the rate of the heterogeneous Cannizzaro reaction is extraordinarily sensitive to changes in the concentration of the base. The reaction of benzaldehyde in contact with 45% aqueous potassium hydroxide is complete in a few hours at room temperature; when 30% aqueous potassium hydroxide is used, several days may be required to effect the same conversion. If the over-all reaction rate showed a first-order dependence on the base concentration, a 33% decrease in the base strength

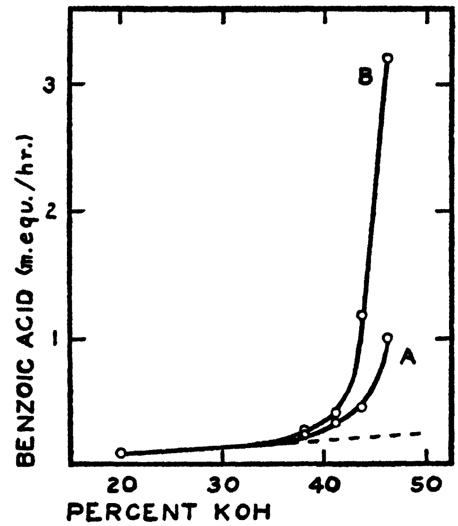


FIGURE 1. EFFECT OF ALKALI CONCENTRATION ON RATE OF CONVERSION

should only decrease the reaction rate by the same factor. Even if the dependency were second-order, the rate of reaction should not be reduced by much more than one-half. The observed decrease in rate under these circumstances is more nearly tenfold.

To study these variations, a series of experiments in which only the initial base concentration was varied was performed. To avoid substantial change in the initial concentrations of the reactants, the reactions were carried only to about 7.5% conversion, and the average rates thus determined were then plotted as a function of the initial alkali concentration (Curve A of Figure 1).

By inspection of the curve it is apparent that in the range of 20–38% potassium hydroxide, and presumably over the range of 0–38%, the reaction is slow and shows a nearly linear dependence on the base concentration. However, at about 38% potassium hydroxide some other factor intervenes to effect a relatively large increase in rate with slight increase in base concentration. The factor responsible for the marked sensitivity of the reaction rate to increasing alkali concentration in this range is the onset of *autocatalysis* by benzyl alcohol.

Autocatalysis of the heterogeneous alkaline dismutation of benzaldehyde by benzyl alcohol. The autocatalytic character of the heterogeneous Cannizzaro reaction (when the critical or a higher concentration of alkali is used) is apparent in a plot of the percentage aldehyde conversion as a function of time. In Figure 2 the variation in rate of reaction of a system initially composed of benzaldehyde and 2.44 molecular equivalents of 46.2% aqueous potassium hydroxide is recorded in this way. Notwithstanding the continuous decrease in the amount of benzaldehyde present and in the alkali concentration, the instantaneous reaction rate, as measured by the slope of the curve, continues to increase beyond 50% conversion. That the continuous increase in the reaction

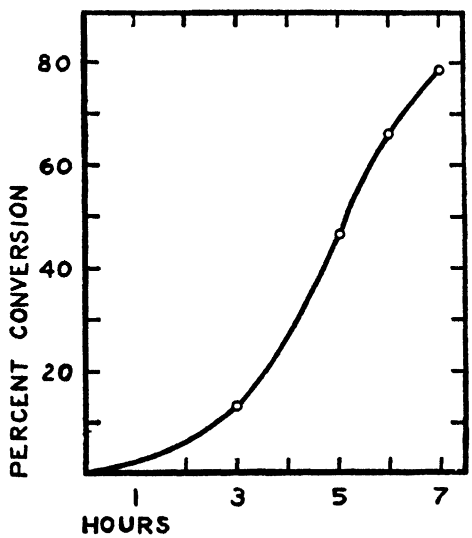


FIGURE 2. AUTOCATALYSIS OF THE HETEROGENEOUS CANNIZZARO REACTION

rate is attributable to the continuous increase in the amount of benzyl alcohol present is shown by the effect of small quantities of added benzyl alcohol upon the initial reaction rate.

In Figure 1, Curve B records a set of experiments performed under the same conditions as the experiments recorded in Curve A except that the benzaldehyde used contained 4 weight percent of benzyl alcohol. It is to be noted that vertically-corresponding points on the two curves were determined for identical reaction periods. In the 20–38% alkali range Curves A and B are experimentally indistinguishable, indicating that in this range the reaction rate is not appreciably affected by small amounts of initially-present benzyl alcohol. Beyond 38% potassium hydroxide concentration the curves diverge rapidly, and the vertical intervals between corresponding alkali-concentration points on the two curves are indicative of the autocatalytic effect of benzyl alcohol.

In the range of alkali concentrations where benzyl alcohol is without catalytic effect the average rate of reaction over the first 7.5% of conversion may fairly well approximate the true initial rate of reaction. The most probable value

for the true initial rate of reaction in the experiments in which autocatalysis occurs is approximated by extrapolation to high alkali concentrations of the rectilinear, coincident portions of Curves A and B of Figure 1.

Locus of the reaction. It is obvious that there is a critical point at which the nature of the reaction changes as the alkali concentration is increased. Understanding of the change must include some knowledge of the reaction site, which, *a priori*, could be in either the liquid phase, at the phase interface, or in some combination of these. In order to ascertain whether or not the over-all reaction rate shows an unequivocal dependence on the volume of either phase, a series of experiments in which a constant volume (5 cc.) of aqueous alkali was agitated with varying volumes (2 cc., 5 cc., 10 cc.) of benzaldehyde was undertaken.

TABLE IV

EFFECT OF VARYING PHASE-VOLUME RATIOS ON OVER-ALL CONVERSION RATE

EXPERIMENT	KOH (5 cc.) CONC'N (%)	C_6H_5CHO (cc.)	TIME (HRS.)	AVERAGE OVER-ALL[a] CONVERSION RATE
I A	20.3	2	13.0	0.095
B		5		.098
C		10		.101
II A	29.6	2	12.0	.131
B		5		.136
C		10		.125
III A	46.2	2	2.0	1.27
B		5		1.21
C		10		1.04
IV A	46.2	2[b]	1.5	0 90
B		5[b]		1.13
C		10[b]		1.44

[a] $d\ C_6H_5CO_2H/dt$, expressed in milliequivalents per hour.

[b] Containing 2 weight percent of benzyl alcohol.

In two sets of experiments in which 20% and 30% potassium hydroxide solutions were used the over-all conversion rates (in terms of milliequivalents of benzoic acid produced per hour) did not vary (beyond the limits of experimental error) with variation in the volume of the benzaldehyde phase. The relevant data are summarized in sections I and II of Table IV. These results imply that at relatively low alkali concentrations the amount of benzaldehyde that disappears depends upon the volume and hydroxyl ion concentration (or activity) of the aqueous phase, and are consistent with the hypothesis that reaction takes place exclusively in the aqueous phase. Under the experimental conditions imposed the rate of diffusion of benzaldehyde into the aqueous phase evidently is not a rate-controlling factor. Other interfacial effects are not necessarily excluded (for the interfacial area presumably varies but little), but there is no evident compulsion to assume such effects.[4]

[4] Supplementary experiments, described later in this discussion showed that interfacial variations do not materially affect the relationships here described.

When the described technique was extended to the reaction with 46.2% potassium hydroxide it became apparent that at higher alkali concentrations the over-all rate of the reaction is no longer determined by the volume and alkali concentration of the aqueous phase (section III, Table IV). Not only had the rate increased out of all proportion to the (first-power) increase in hydroxyl ion concentration of the aqueous phase; it now showed an inverse dependence on the volume of the benzaldehyde phase. These facts suggest the initiation of a catalyzed concurrent reaction in the benzaldehyde phase.

In a fourth series of experiments, varying volumes of benzaldehyde containing 2 weight percent of benzyl alcohol were treated with a fixed volume of 46.2% aqueous potassium hydroxide (section IV, Table IV). The over-all rate of reaction then showed an increase with increasing benzaldehyde volume.

These observations are consistent with the hypothesis that: (a) at all alkali concentrations there is a relatively slow[5] hydroxide ion-catalyzed reaction in the aqueous phase, the rate of which is limited by the solubility of benzaldehyde in that phase; (b) above a critical alkali concentration of the aqueous phase there is a concurrent relatively rapid[5] benzylate ion-catalyzed reaction in the benzaldehyde phase.

Re-examination of the data of sections III and IV of Table IV in the light of the proposed hypothesis may serve to clarify and substantiate the foregoing statement. In the absence of benzyl alcohol the dismutation of benzaldehyde begins in the aqueous phase, and in the early stage of the reaction benzyl alcohol is produced at the same rate regardless of the volume of the benzaldehyde phase. As the concentration of benzyl alcohol builds up, however, and benzylate ions are transferred to the benzaldehyde phase, the *concentration* of benzylate ions, which determines the rate of reaction in the non-aqueous phase is initially greater when the benzaldehyde volume is small, and correspondingly smaller when the benzaldehyde phase is large. For low percentage conversions, therefore, the over-all rate of conversion for the "heterogeneous" reaction is greater when the aldehyde phase is relatively small and less when the benzaldehyde phase is relatively large (section III, Table IV).

When a constant small amount of benzyl alcohol is initially present in the benzaldehyde, the two phase reactions proceed concurrently from the first, and the over-all rate of conversion ($d\ C_6H_5CO_2H/dt$) for small percentage conversions is greatest when the benzaldehyde phase is largest (section IV, Table IV). As the reaction proceeds, and as the benzylate ion concentration is increased more rapidly by transfer from the aqueous phase into the smaller benzaldehyde phase, the over-all rates of conversion in the three experiments should tend to converge.

That the nature and extent of the interfacial area do not materially affect any rate-determining step of the over-all reaction was shown with the aid of emulsifying agents. Although not ideal, fatty acid soaps were used as emulsifiers and proved fairly effective. In 46% alkali solution, potassium stearate and lau-

[5] "Slow" and "rapid" are here used in the special sense implying contribution to the over-all reaction rate in terms of $d\ C_6H_5CO_2H/dt$.

rate were without perceptible effect on the over-all rate. In more dilute alkali solution, potassium laurate did increase the rate of reaction, but only by increasing the solubility of benzaldehyde in the aqueous phase.

Abnormal differences in reaction rates of substituted benzaldehydes. It is well known that substituted benzaldehydes undergo the homogeneous Cannizzaro reaction at varying rates (3). According to Weissberger and Haase (13) the homogeneous reaction rates of the *meta-* and *para*-substituted benzaldehydes may be related to the acid dissociation constants of the respective corresponding benzoic acids (the *ortho*-substituted benzaldehydes exhibit an "ortho effect"). In the heterogeneous reaction the relative reactivities of the aldehydes fall in the same order, but the differences in over-all rates of conversion are greatly exaggerated. For example, the data of Molt (3) indicate that in methanol at 100° the third-order constant for the rate of reaction of benzaldehyde with

TABLE V

EFFECT OF ADDED BENZYL ALCOHOLS ON OVER-ALL RATE OF REACTION OF BENZALDEHYDE WITH 46.2% AQUEOUS POTASSIUM HYDROXIDE

ADDED ALCOHOL	TIME (MIN.)	% CONVERSION
None	60	4.1
Benzyl	60	15.6
p-Nitrobenzyl	60	48.1
None	100	11.2
Anisyl	100	28.9
Benzyl	100	43.7
p-Chlorobenzyl	100	48.6

sodium hydroxide is greater than that of anisaldehyde for the analogous reaction by a factor of 20–25. In the heterogeneous reaction with 46% aqueous potassium hydroxide, the initial over-all rate of conversion for benzaldehyde is rapid, whereas that for anisaldehyde is almost negligibly slow, the difference factor being estimated as of the order of 200–500.[6] *p*-Nitrobenzaldehyde, on the other hand, is more reactive than benzaldehyde.

Taken in conjunction with the facts set forth in the foregoing discussion, these observations suggest that the respective benzylate ions differ considerably in their ability to catalyze the aldehyde-phase reaction. In two sets of experiments designed to test this point small constant molar percentages of several benzyl alcohols were added to samples of benzaldehyde, which were then treated with 46% aqueous potassium hydroxide (Table V).

The catalytic effectiveness of the respective benzylate ions would appear to be related to the probable acidities of the respective alcohols.

Assuming that the abnormally low reactivity of anisaldehyde in the heterogeneous reaction with 46% aqueous potassium hydroxide is attributable to

[6] It should be noted that the quantities mentioned, namely, the third-order rate constant (k) for the homogeneous reaction and the overall rate of conversion ($d\ RCO_2H/dt$) for the heterogeneous reaction, are not directly comparable.

the relatively feeble autocatalytic properties of the anisylate ion, it should be possible to accelerate the conversion by the addition of suitable aldehyde-phase reaction catalysts. This possibility was realized in two sets of experiments summarized in Table VI.

Methanol and benzyl alcohol proved relatively weak accelerators; the glycols tested were much more effective. Phthalyl alcohol and phenylethylene glycol are probably even better than the data of Table VI would indicate, for in the quantities used they were not completely soluble in anisaldehyde. It seems likely that with suitable catalysts the heterogeneous conversion of other relatively unreactive aldehydes could be accelerated.

TABLE VI

EFFECT OF ALDEHYDE-PHASE CATALYSTS ON THE RATE OF CONVERSION OF ANISALDEHYDE IN THE PRESENCE OF 46.2% AQUEOUS POTASSIUM HYDROXIDE

CATALYST, MOLE %[a]	TIME (HOURS)	% CONVERSION
None	28	0.95
Benzyl alcohol, 5.0	28	2.24
Phthalyl alcohol, 5.0	28	5.38
1-Phenyl-1,3-propanediol, 5.3	18	22.8
1-Phenyl-1,3-propanediol, 11.5	18	50.9
None	70	5.65
Methanol, 12.2	70	3.84
Methanol, 24.4	70	6.08
Methanol, 36.6	70	20.8
Phenylethylene glycol, 11.5	70	74.3

[a] Based on moles of anisaldehyde used.

DISCUSSION

Concerning the major problems peculiar to the heterogeneous Cannizzaro reaction (as outlined in the Introduction) the following facts have been established.

1. Unlike the homogeneous reaction, the heterogeneous Cannizzaro reaction is remarkably susceptible to the catalytic effects of small amounts of polyhydroxy compounds ordinarily present as impurities in benzaldehyde that has been aged under ordinary laboratory conditions.

2. Benzyl alcohol, although a much less effective catalyst than some of the glycols investigated, is responsible for the autocatalytic character of the heterogeneous benzaldehyde Cannizzaro reaction when highly concentrated alkaline solutions are used.

3. The alcoholic (or glycolic) catalysts function by effecting an aldehyde-phase reaction which contributes much more toward the over-all rate of conversion than does the concurrent aqueous-phase reaction.

4. The marked variation in the reactivity of substituted benzaldehydes is largely due to the relative catalytic efficiencies of the corresponding benzylate ions.

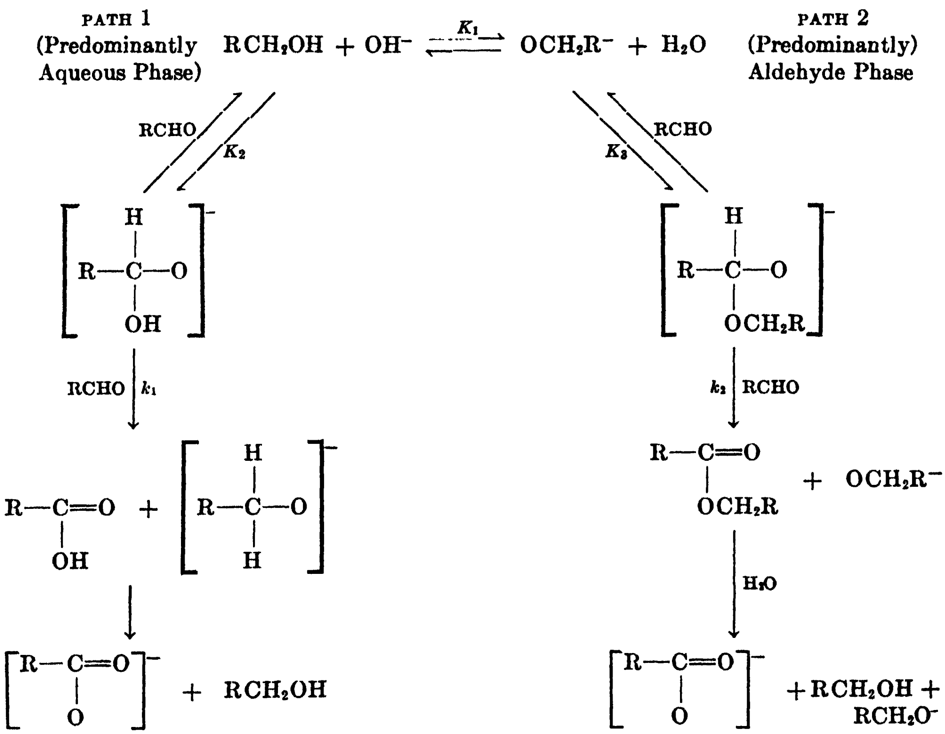
5. The rate of conversion of relatively unreactive aldehydes (such as anisaldehyde) may be materially accelerated by suitable catalysts.

Proposed reaction scheme, and some verifiable implications thereof. These facts, together with the results of kinetic studies of the homogeneous Cannizzaro reaction, supply a basis for the formulation of the proposed reaction scheme outlined in Diagram I.

At all alkali concentrations the reversible metathetical reaction, to which the equilibrium constant K_1 has been assigned, takes place. Within the limits of

DIAGRAM I

PROPOSED REACTION SCHEME FOR THE HETEROGENEOUS ALKALINE DISMUTATION OF AROMATIC ALDEHYDES



solubility of the components, the extent of displacement of the equilibrium toward the right will be determined primarily by the acidity of the alcohol (RCH_2OH) and the concentration of the hydroxyl ion. At low alkali concentrations the metathetical reaction has no significant effect upon the rate of conversion of aldehyde. There is negligible diffusion of alkoxide ions into the non-aqueous phase, and conversion by Path 2 in the aqueous phase must be very slight, and may proceed at a rate not greatly different from that of conversion by Path 1. At higher alkali concentrations the relative solubilities of alkoxide ion in the aqueous and non-aqueous phases alter sharply, and there is

partial, or perhaps even preferential, distribution in the non-aqueous phase. Disproportionation of aldehyde to ester then takes place rapidly in the non-aqueous phase. The total concentration of alkoxide ions is further increased by hydrolysis of the ester, in part by diffusion of water into the aldehyde phase, but probably much more by diffusion of ester to the interface or into the aqueous phase.

The over-all conversion rate implied by the reaction scheme suggested in Diagram I may be defined by the expression:

$$d\,(\mathrm{RCHO})/dt = k_1\,(\mathrm{OH^-})\,(\mathrm{RCHO})^2 + k_2\,(\mathrm{OCH_2R^-})\,(\mathrm{RCHO})^2.$$

No attempt has been made as yet to estimate the relative values of k_1 and k_2, but is is evident that if k_1 is not enormously greater than k_2 the rate of conversion by Path 2 will greatly exceed the rate of conversion by Path 1, which is sharply limited by the solubility of the aldehyde in the aqueous phase.

Apparent conflicts in hitherto available evidence as to whether or not benzyl benzoate is an intermediate in the alkaline dismutation of benzaldehyde are satisfactorily resolved by the reaction scheme proposed (Diagram I). In essentially aqueous-phase reactions the ester is a possible, but not a necessary intermediate. In view of the rapidity with which benzyl benzoate undergoes saponification (2a) it would not be an isolable intermediate. In essentially non-aqueous-phase reactions the ester is a probable (though again not a necessary) intermediate. Under properly chosen conditions it is unquestionably isolable.

It was shown in section III of Table IV that in the early stages of the heterogeneous dismutation of benzaldehyde by 46% aqueous potassium hydroxide there is a slight inverse dependence of the over-all rate of conversion on the volume of the aldehyde phase. The kinetic scheme outlined in Diagram I requires that all experiments in section III of Table IV should show the same over-all rate. (This follows from the fact that during the early stage of the reaction the same amount of benzyl alcohol will be present in all reaction mixtures, owing to the fixed volume of the aqueous phase. The concentration of benzylate ion in the oil phase will then vary inversely as the volume of the oil phase. However, the over-all amount of reaction in the oil phase depends upon the product of the benzylate concentration and the volume of benzaldehyde, and therefore should remain constant in all experiments.) The discrepancy between the theory and the experimental results is to be attributed to a differential in the time lag involved in hydrolyzing benzyl benzoate to the catalytically effective benzyl alcohol. This is borne out by the fact that addition of potassium laurate to a similar series of reaction mixtures (to facilitate equilibrium between the two phases) brings the results in closer accord with theory, as shown in Table VII.

In section IV of Table IV a different situation prevails, and it is to be noted that initially the over-all rate of reaction by Path 2 (Diagram I) will vary directly as the volumes of benzaldehyde present (for the benzylate ion concentration will be the same in the benzaldehyde). However the constant increment of benzyl alcohol contributed by the aqueous phase exerts a leveling effect, and the total over-all rates of reaction converge with increasing conversion.

According to the reaction scheme proposed (Diagram I), the effectiveness of a hydroxylic compound as a catalyst for the heterogeneous Cannizzaro reaction must depend upon: (a) the facility with which it forms alkoxide, and (b) the possibility of transfer of the alkoxide to the aldehyde phase. For a given alkali concentration, the first of these factors is a function of the acidity of the hydroxylic compound. The second is a function of the distribution coefficient, which is to say, of the solubilities in the aqueous and aldehydic phases, respectively.

For structurally similar alcohols (whose alkoxides presumably would not differ greatly in solubility properties), the relative acidities should be the controlling factor. This has already been seen to be true of the benzyl alcohols (Table VI). Supplementary experiments with a variety of miscellaneous alcohols (Table VIII) tend to substantiate this view. For example, the strongly acidic phenol is an excellent catalyst, the mildly acidic benzyl alcohol a fair catalyst, and the very weakly acidic *t*-butyl alcohol and benzohydrol are substantially ineffective.

TABLE VII

OVER-ALL RATES OF CONVERSION OF VARYING VOLUMES OF BENZALDEHYDE BY 46.2% AQUEOUS POTASSIUM HYDROXIDE (5 CC.) IN THE PRESENCE OF POTASSIUM LAURATE (47.6 MG.) IN TWO HOURS

VOL. C_6H_5CHO (CC.)	d $C_6H_5CO_2H$ (MILLI EQUIV. PER HR.)
2	0.93
5	1.02
10	1.05

Relative solubilities, however, exert a modifying effect on the behavior of structurally dissimilar alcohols. At first thought it might seem improbable that a salt would undergo appreciable distribution between an aqueous phase and a relatively non-polar non-aqueous phase. There is reasonable question, however, that 46% aqueous potassium hydroxide should be regarded as an essentially aqueous medium. Thermodynamic studies by Akerlof and Bender (14) indicate that at high alkali concentrations—*i.e.*, about 7 *molal* (31%), or higher—there is a "structural constancy" of the solutions. In other words it is doubtful that such solutions contain any "free" water at all.

It was noted visually in the course of this study that catalytically effective alkoxides, although often soluble in water, are virtually insoluble in concentrated aqueous potassium hydroxide solutions. On the other hand, it was found that the potassium salts of some catalytically ineffective polyhydroxy compounds, which must be relatively acidic (*e.g.*, ethylene glycol, glycerol, pinacol), are not salted out of concentrated alkali solutions.

It was found that the highly effective catalyst potassium phenolate is very slightly soluble in concentrated aqueous potassium hydroxide solution, from which it separates as the dihydrate. The dihydrated salt dissolves readily in

TABLE VIII

EFFECT OF MISCELLANEOUS HYDROXY COMPOUNDS ON RATE OF HETEROGENEOUS REACTION OF BENZALDEHYDE (5 CC.) WITH 46.2% AQUEOUS POTASSIUM HYDROXIDE (5 CC.)

COMPOUND, MOLE %	TEMP. (°C)	TIME (HRS.)	% CONVERSION
None	24.0	2.25	8.2
Methanol, 4.00			11.6
n-Amyl alcohol, 4.00			33.7
Lauryl alcohol, 4.00			39.1
None	26.2	2.25	8.9
Methanol, 6.00			23.4
n-Amyl alcohol, 6.00			62.4
None	27.5	2.25	11.2
Methanol, 8.00			71.0
n-Amyl alcohol, 8.00			67.8
Isopropyl alcohol, 8.00			37.1
Benzyl alcohol, 3.92	25.0	1.40	34.3
Methanol, 13.24			69.9
n-Amyl alcohol, 4.80			20.7
t-Butyl alcohol, 5.72			6.3
Benzyl alcohol, 3.92	27.0	1.00	19.8
Benzyl alcohol, 19.60			59.6
n-Amyl alcohol, 4.80			15.8
n-Amyl alcohol, 24.00			54.3
None	24.0	3.00	12.1
Benzyl alcohol, 3.92			78.6
Benzohydrol, 2.32			14.0
None	25.0	3.00	12.8
Phenylbenzylmethanol, 2.16			11.4
α-Phenylethanol, 3.48			11.0
Phenethyl alcohol, 3.48			51.7
None	25.0	3.00	10.6
Hydrocinnamyl alcohol, 2.00			38.9
Phenethyl alcohol, 3.48			61.8
None	24.5	2.00	7.2
Phenethyl alcohol, 3.48			37.0
Benzyl alcohol, 3.92			48.6
Phthalyl alcohol, 3.08			88.5
None	26.9	2.75	21.2
Phenol, 4.20			68.9
Stearyl alcohol, 3.70[c]			28.9

TABLE VIII—*Concluded*

COMPOUND, MOLE %	TEMP. (°C)	TIME (HRS.)	% CONVERSION
None	25.0	2.00	7.8
Stearyl alcohol, 1.48			9.4
1,10-Decanediol, 2.44			23.0
Oleyl alcohol,[a] 0.16			41.6
None	24.5	2.00	6.5
Oleyl alcohol,[b] 0.16			5.8
None	24.5	2.10	5.3
Oleyl alcohol,[b] 0.32			10.1
Oleyl alcohol,[a] 0.32			62.8
None	26.0	3.00	11.0
Cumene hydroperoxide, 0.14			15.1
None	26.0	2.00	6.8
Tung oil, 4.0[d]			37.0
Linseed oil, 4.0[d]			41.9

[a] Containing peroxides.
[b] Peroxide-free.
[c] Incompletely soluble.
[d] Weight percent.

benzaldehyde at room temperature and initiates a rapid exothermic reaction which yields potassium benzoate and benzyl alcohol. The anhydrous salt is not appreciably soluble in benzaldehyde at room temperature, but at 100° catalyzes a reaction which yields benzyl benzoate.

EXPERIMENTAL

Purification of aldehydes. Commercial *benzaldehyde* (Merck's N.F. quality) in five-pound brown bottles, used as a source of supply, was always kept under nitrogen in a dark closet. The methods of purification of the benzaldehyde were essentially the same as those used by Chenicek (10), Foy (9), and Richlin (11). The benzaldehyde to be used in any given set of experiments was always purified immediately before use. A 100-cc. portion was washed with two 10-cc. portions of 10% aqueous potassium hydroxide (to remove phenolic antioxidants and benzoic acid) and with two 10-cc. portions of a saturated sodium sulfite solution (to remove peroxidic materials), was dried over sodium sulfate under nitrogen in the dark, and was then transferred to a distillation apparatus. The distillation apparatus consisted of two 125-ml. flasks connected by a yoke of 18-mm. glass tubing. A side-arm of 10-mm. tubing was inserted at the center of the yoke to permit connection to the vacuum line. The benzaldehyde which had been placed in one bulb of the distillation apparatus was cooled to −80°, and the apparatus was then evacuated to about 10^{-5} mm. pressure. The benzaldehyde was degassed by the usual vacuum-line technique. It was then distilled from the one bulb to the other by cooling the second bulb to −80° while allowing the first bulb to warm to room temperature. The distillation and subsequent operations with the aldehyde were carried out in the dark.

The purification of *anisaldehyde* was carried out in a manner similar to that described for benzaldehyde.

Preparation of potassium hydroxide solution. Potassium hydroxide stock solutions varying in concentration from 20 to 53% were prepared by dissolving the requisite quantities of U.S.P. potassium hydroxide pellets (containing *ca.* 3% of potassium carbonate) in freshly boiled distilled water. The solutions were standardized by titration with standard acid, using phenolphthalein indicator, and were stored in Pyrex bottles which had previously contained strong alkali solutions. The potassium hydroxide solutions were standardized from time to time to ascertain whether the normality decreased owing to attack on the glass; no changes were ever noted.

Purity of compounds tested for catalytic activity. The melting points of all crystalline compounds were determined and compared with those recorded in the literature. Liquid compounds were distilled prior to use.

Preparation of potassium phenolate. The preparation of potassium phenolate requires special mention because of its novelty as a reagent. The *dihydrate* was prepared by adding 40% aqueous potassium hydroxide to molten phenol at 60–70° to the point of incipient precipitation. On cooling to 0° the salt crystallized in large white plates which were filtered and washed successively with 20% aqueous potassium hydroxide, a small quantity of water, and ether The crystals were allowed to stand in a desiccator over calcium chloride before use

Two different methods were used to prepare ***anhydrous*** potassium phenolate.

(A) Distilled phenol (94 g., 1 mole) contained in a 150-cc. flask was heated to 45°. The air in the flask was displaced by nitrogen; 3.9 gms. (0 1 mole) of potassium metal was then added to the phenol. To avoid too violent a reaction it was necessary to cool the reaction intermittently with a Dry Ice–ether bath while the potassium dissolved. The temperature should be maintained somewhere between the melting points of phenol and potassium Aliquot samples of this stock solution of potassium phenolate in phenol were transferred to empty reaction vessels, and the excess of phenol was removed by evaporation at reduced pressure (10^{-3} mm.).

(B) To distilled phenol (141 g., 1.5 mole) contained in a 250-cc. flask under a nitrogen atmosphere and heated to 45° was added 33.6 g. of a 50% aqueous potassium hydroxide solution Suitable aliquots of this stock solution were pipetted into reaction vessels, and the water and excess phenol were removed at reduced pressure. To insure the complete absence of water additional molten phenol was added to the residue, and the phenol was again removed by distillation at 10^{-3} mm. and 130°. This procedure yielded potassium phenolate which was considered satisfactory for experimental purposes.

Methods of operation. All the Cannizzaro reactions with aqueous potassium hydroxide recorded in this paper were carried out in Pyrex glass tubes (120 × 18 mm.). The reactants were pipetted into the reaction tubes which had been previously swept out with nitrogen. The denser alkali solution was added first and then frozen in a Dry Ice–chloroform bath to prevent premature mixing with the aldehyde. The additive, if any, and the aldehyde were next added, and the reaction mixture was chilled to −80°. The vessel was then evacuated, and the reactants were degassed, after which the tube was sealed off. The reaction mixtures were then warmed to room temperature and agitated in a horizontal position on a horizontal shaking machine with a frequency of about 200 cycles per minute.[7]

Method of analysis. The percentage conversion was followed by determination of the amount of *benzoic acid formed.* The reaction vessels were opened, and the contents were transferred to 100-ml. separatory funnels. The reaction mixtures were each extracted with three 50-cc. portions of ether to remove benzyl alcohol and unchanged benzaldehyde. The alkaline solutions were then acidified with hydrochloric acid and reextracted with three 50-cc. portions of ether. The latter ether extracts were evaporated to dryness in tared

[7] Thermostatic control of the reaction temperature was not employed because, until the factors affecting the rate of reaction had been elucidated, it was thought that valid comparisons could be made only among individual experiments of a set which were run simultaneously.

flasks, dried in a vacuum desiccator overnight and then weighed. Occasionally the results of this gravimetric analysis were checked by titrating the weighed acid with standard base; no disagreement was ever noted. Experiments with known mixtures have indicated that the method is accurate to within ±3%.

CANNIZZARO REACTIONS WITH POTASSIUM PHENOLATE

(a) *Potassium phenolate dihydrate.* To 21.2 g. (0.2 mole) of benzaldehyde, contained in a 50-cc. flask under nitrogen, was added 16.8 g. (0.1 mole) of potassium phenolate dihydrate. The resultant solution rapidly warmed to about 50° and almost immediately a bulky precipitate of potassium benzoate appeared. No attempt was made at a quantitative estimation of the degree of conversion, but both benzoic acid and benzyl alcohol were identified as reaction products [The benzyl alcohol was isolated by extraction of the reaction product with water, treatment of the remaining oil with sodium bisulfite (to remove excess benzaldehyde), further washing of the residue with alkali solution (to remove phenol), followed by distillation].

(b) *Anhydrous potassium phenolate.* To 1.32 g. (0.01 mole) of anhydrous potassium phenolate, contained in a 50-cc. flask, was added 50 g. (0.47 mole) of benzaldehyde. The flask was sealed off and was then heated at 100° for 18 hours. The reaction products were worked up as follows. The reaction mixture was filtered, and the filtrate was distilled in a Hickman still to remove residual salts. The distillate was redistilled through a Vigreaux distilling-column at 10 mm. pressure to yield 15 g. of benzyl benzoate (m.p. 19°). The ester was further identified by its refractive index and saponification equivalent.

The incomplete conversion of aldehyde to ester is attributable to the fact that a small amount of condensation to form resins occurs between phenol and benzaldehyde under the reaction conditions employed, the net effect of which is to destroy the catalyst. It is believed that a more careful search for optimum reaction conditions would lead to quantitative conversions.

SUMMARY

1. The heterogeneous Cannizzaro reaction has been investigated, and the following problems peculiar to it have been explained:

(a) the anomalous variations in reaction rate with differences in the origin and history of the aldehyde; (b) the abnormal sensitivity of the reaction rate to changing alkali concentration; (c) the influence of autocatalysis on the reaction rate; (d) the locus of the reaction; and (e) abnormal differences in the reaction rates of substituted benzaldehydes.

2. The Cannizzaro reaction is shown to occur exclusively in the aqueous phase at low alkali concentrations.

3. At high alkali concentrations a concurrent, but much faster, oil-phase conversion is shown to take place.

4. The oil-phase reaction is shown to be subject to catalysis by some alcohols and glycols, and the conditions for catalytic effectiveness are set forth.

5. A comprehensive mechanism to explain all the known facts about the Cannizzaro reaction is outlined.

6. Potassium phenolate dihydrate is shown to be an effective reagent for the dismutation of benzaldehyde to the conventional Cannizzaro reaction products.

7. Anhydrous potassium phenolate is shown to be an effective catalyst for the conversion of benzaldehyde to benzyl benzoate.

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[Contribution No. 56 from the Institute for Atomic Research, and the Department of Chemistry, Iowa State College]

THE SYNTHESIS OF 1,2-CYCLOHEPTANEDIONE DIOXIME[1]

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The successful application of 1,2-cyclohexanedione dioxime (Nioxime) to the analytical chemistry of nickel and palladium by Voter, Banks, and Diehl (1, 2) led naturally to the study of cyclic homologs of this compound as analytical reagents. Preliminary studies of 1,2-cyclopentanedione dioxime and 1,2-cycloheptanedione dioxime indicated that the former was of no value in this connection, but that the latter possessed certain properties that warranted its further consideration. The object of the work reported here was to develop the preparation of 1,2-cycloheptanedione dioxime so as to make it available to the analyst for more extended study and use.

Godchot and Cauquil (3) obtained 1,2-cycloheptanedione dioxime as a derivative of 1,2-cycloheptanedione, which they prepared by oxidation of cycloheptanone with selenium dioxide in an alcoholic medium. No further experimental details are given by them for either the diketone or the dioxime preparation.

Rauh, Smith, Banks, and Diehl (4) have outlined three methods of attack for the preparation of 1,2-cyclohexanedione dioxime, all of which should be applicable here if cycloheptanone is used as the starting material instead of cyclohexanone. The first is the Riley oxidation of cyclohexanone with selenium dioxide, followed by oximation. The second is the method of Jaeger and van Dijk, which was attempted by Rauh, *et al.*, and employed more successfully by Geissman and Schlatter (5). This involves the condensation of cyclohexanone with diethyl oxalate to give cyclohexanoneoxalylic ester, which is then pyrolyzed to cyclohexanonecarboxylic ester. The carboxylic ester is converted into 1,2-cyclohexanedione monoöxime by shaking with alkali and sodium nitrite in the absence of air, followed by acidification. The dioxime is prepared by oximation of the monoöxime. The third procedure consists in the more direct preparation of the monoöxime through the action of 2-ethyl-*n*-hexyl nitrite on cyclohexanone, with subsequent oximation to the dioxime.

The simplicity of the selenium dioxide oxidation method and the fact that the oxidizing reagent can be largely recovered made this procedure at once the most attractive of those considered. We concentrated on this method, therefore, and obtained quite satisfactory yields from it.

Cycloheptanone is available commercially, but at a price that permits only very limited use. Cycloheptanone is easily prepared by the dry distillation of the calcium or thorium salt of suberic acid (6), but the latter material is also prohibitively expensive, in the quantities that were needed. We found it economically advantageous to prepare cycloheptanone by the method of Meerwein (7), as utilized and improved by Kohler, Tishler, Potter, and Thompson (8). This in-

[1] This document is based on work performed in the Ames Laboratory of the Atomic Energy Commission

volves the ring enlargement of cyclohexanone through the action of diazomethane, which is produced in the reaction vessel by the decomposition of nitrosomethylurethan. Nitrosomethylurethan was prepared from ethyl-N-methylcarbamate by the method of Hartman and Phillips (9); ethyl-N-methylcarbamate was synthesized according to the directions of Hartman and Brethen (10).

The following procedures for the preparation of 1,2-cycloheptanedione and 1,2-cycloheptanedione dioxime were found to give the best yields.

EXPERIMENTAL

1,2-Cycloheptanedione. A solution of 336 g. (3.0 moles) of cycloheptanone in 700 ml. of absolute ethyl alcohol was placed in a 5-liter flask. The latter was fitted with a Glascol mantle, a reflux condenser, and a dropping-funnel. A solution of 333 g. (3.0 moles) of sublimed selenium dioxide, prepared by the method of Riley and Gray (11), in a mixture of 500 ml. of absolute ethyl alcohol and 1600 ml. of 95% ethyl alcohol was placed in the dropping-funnel. The cycloheptanone-alcohol solution was heated to refluxing and then the selenium dioxide solution was added over a period of one and one-quarter hours. The resultant mixture was refluxed for an additional six hours, allowed to stand at room temperature for about eighteen hours, and then filtered. About one liter of alcohol was distilled from the filtrate at atmospheric pressure; the residue was then filtered again, and the distillation continued under reduced pressure. The diketone came over as a deep yellow liquid; yield 340 g. (90%), b.p. 107–109°/17 mm.

1,2-Cycloheptanedione and water were observed to form a constant-boiling mixture; the absolute alcohol-95% alcohol mixture was used as the solvent in order to separate the water from the diketone in the distillation. The use of this mixture materially increased the yield.

The selenium separated by the filtrations (80% or better was recovered in most of the runs) was in suitable condition, after washing and drying, for reoxidation and reuse. That which remained in the reaction mixture through the distillation could not be used again for it was contaminated with organic material that could not be washed out, and attempts to reoxidize it resulted in explosively violent reactions.

Over a period of several weeks, 1,2-cycloheptanedione decomposes and darkens noticeably; consequently it should be used soon after its preparation.

1,2-Cycloheptanedione dioxime. Separate solutions of 139 g. (2.0 moles) of hydroxylamine hydrochloride in 250 ml. of water and 80 g. (2.0 moles) of sodium hydroxide in 150 ml. of water were prepared, cooled below 5°, and mixed in a 3-liter beaker immersed in an ice-salt-water bath. Then 200 ml. of methyl alcohol was added to this solution. A solution of 63 g. (0.50 mole) of 1,2-cycloheptanedione in 400 ml. of methyl alcohol was placed in a 500-ml. separatory funnel suspended above the beaker. When the solution in the beaker had cooled below 0°, the diketone solution was added slowly, with rapid mechanical stirring, over a period of one and one-half hours. The stirring was continued for twenty-four hours, the reaction mixture being allowed to warm to room temperature as the ice in the bath melted. At the end of this period, the ice and salt in the bath were replenished and the reaction mixture was cooled below 0° for two hours. The crystalline precipitate was filtered off, and the filtrate was distilled under reduced pressure until tarry bubbles started to form on the surface of the liquid. The distillation was stopped, and the mixture was extracted hot with two 100-ml. portions of petroleum ether (Skellysolve D, b.p. range 75–120°), which removed the tarry bubbles. The aqueous phase was cooled to 0° and filtered to remove additional dioxime. About 150 ml. of water was added to the filtrate, which was then evaporated to about 350 ml., cooled to 0°, and filtered to remove the final crop of dioxime. On some runs it was found necessary to repeat the hot petroleum ether extraction because of the second appearance of tarry bubbles during the evaporation. The extraction process serves to separate unreacted and decomposed diketone from the reaction mixture,

and a much purer product is obtained. The crystalline product was recrystallized from water; yield 36 g. (46%), m.p. 179–180°.

1,2-Cycloheptanedione dioxime crystallizes from water with one molecule of water; this is lost at 85–87°. Recrystallization from benzene (convenient for the recrystallization of small amounts only), yields the anhydrous dioxime, m.p. 182°.

Anal. (recrystallized from benzene). Calc'd for $C_7H_{12}N_2O_2$: N, 17.94.
Found: N, 17.75, 17.90.

Acknowledgment. The authors wish to express their gratitude to Richard Ewing, who performed the analyses.

SUMMARY

A method has been devised for the preparation of 1,2-cycloheptanedione dioxime in amounts large enough to be useful in inorganic analytical application. The scheme involves oxidation of cycloheptanone to 1,2-cycloheptanedione with selenium dioxide, and conversion of the diketone to the dioxime with hydroxylamine. An over-all yield of 40% is obtained.

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SOME DERIVATIVES OF AMIDONE

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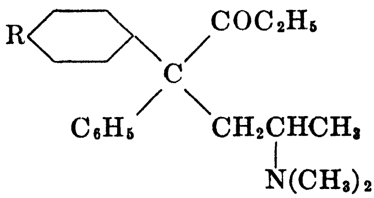
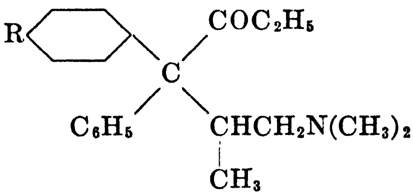
Since the biological properties of amidone (I, R = H) became known (1) only Thorp, Walton, and Ofner (2) have investigated systematically the influence of structural changes on the activity of the molecule; they condensed diphenylacetonitrile with aminoalkyl chlorides other than dimethylaminopropyl chloride and treated the condensation products with Grignard reagents other than ethylmagnesium bromide. In the present paper, variations in the diphenylmethyl moiety of the amidone molecule have been studied; the *p*-methoxy, *p*-methyl, and *p*-bromo derivatives of amidone (I, R = OCH_3, CH_3, Br, respectively) and its fluorene analog, 9-(β-dimethylaminopropyl)-9-propionylfluorene (II) have been prepared as well as 4,5-diphenyl-4-(β-dimethylaminopropyl)-3-pentanone (III), in which one of the phenyl groups of the amidone molecule is replaced by the benzyl radical.



I



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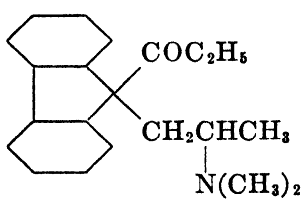

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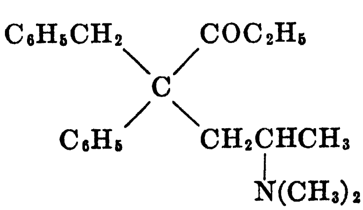
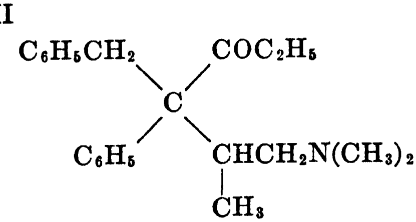


III

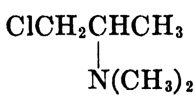


IIIa

It was expected that these experiments would shed some light on the conditions of the simultaneous formation of the two isomers (I, Ia, R = H) which are obtained in the case of amidone[1] (3, 4) when diphenylacetonitrile is con-

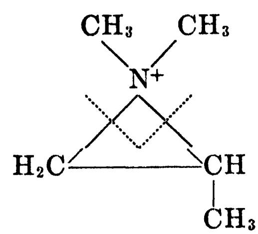
[1] Easton, *et al.* (3), have also described a third isomeride of amidone, the structure of which has not yet been elucidated.

densed with either 2-dimethylamino-1-chloropropane (IV) or 1-dimethylamino-2-chloropropane (V), a fact which Schultz and Sprague (5) very plausibly ascribe to the transitory formation, from both (IV) and (V), of the ion (VI), capable of fission in two different ways (6, 7, 8). The diphenylacetonitrile anion causes this fission to take place in both directions to roughly the same extent. Our own observations have led to the same conclusion for the three *p*-substituted diphenylacetonitriles and for phenylbenzylacetonitrile: they lead to mixtures of the two isomers independently of whether (IV) or (V) is used as starting material. The only exception to this rule was observed in the synthesis of the fluorene derivative (II), in which only one product was obtained in excellent yield; the corresponding 9-(β-dimethylaminopropyl)-9-cyanofluorene—which is an oil—must, therefore, also have been a homogeneous substance.

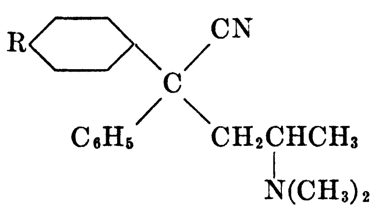


IV

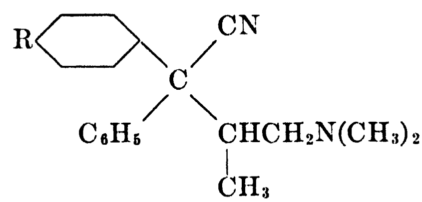
V



VI



VII



VIIa

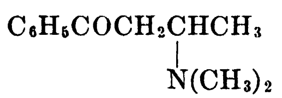
This may be due to the more pronounced acidic character of 9-cyanofluorene, as compared with diphenylacetonitrile and its derivatives, which causes one path of attack on (VI) to be preferred to the other in the same way as the chloride ion prefers the fission VI → V to VI → IV (5); the compound (IV) can thermally rearrange to (V), but not *vice versa*.

The nitriles (VII) and (VIIa) (R = OCH_3, CH_3, Br) and the nitrile corresponding to (III) and (IIIa), although analytically pure, did not crystallize and could not be separated into their constituent isomerides. They were treated with ethylmagnesium bromide and gave, upon subsequent hydrolysis, mixtures of the two isomeric ketones. In order to separate them, the—apparently quite different—basicity of the isomerides was utilised: when the mixtures were treated with half the theoretical amount of hydrochloric acid, one of the isomeric hydrochlorides precipitated; its purity (after recrystallization) was established by its crystallographic homogeneity, the sharpness of its melting point, and the possibility of its conversion into a homogeneous picrate. In no case has it been possible to isolate the second isomer, too, in a pure crystalline state.

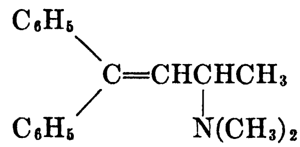
In the reaction of the nitriles (VII) and (VIIa) with ethylmagnesium bromide, the ketimines corresponding to (I) and (Ia) are formed initially; we have observed that the hydrolysis did not necessitate as stringent conditions as have been applied in the case of amidone and its isomer.

The impossibility of isolating both isomerides made it desirable to determine the side-chain structure of the crystalline products obtained. Of the three methods used hitherto in this series—that of Schultz, Robb, and Sprague (4); that of Easton, Gardner, and Stevens (9); and that of May and Mosettig (10)—the last seemed most adequate.

This method consists essentially in degradation through 3-dimethyl-1,1-diphenylbutane to 1,1-diphenylbutane; the latter was synthesized by an unambiguous method. The former has now been synthesized by an unambiguous method[2] of more general application, *viz:* by conversion of propenyl phenyl ketone to β-dimethylaminobutyrophenone (VIII) with dimethylamine, reaction of VIII with phenylmagnesium bromide, dehydration of the resulting carbinol to the olefin (IX), and catalytic hydrogenation of the latter.

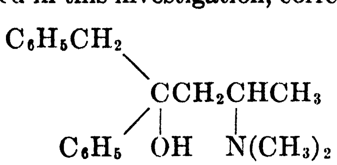


VIII

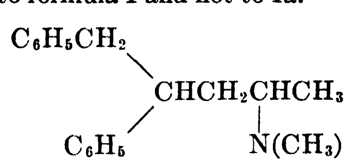


IX

By application of this method, it was, *e.g.*, possible to prove the structure (III) for the crystalline benzyl compound. Reaction of VIII with benzylmagnesium chloride gave the carbinol (X) which, by dehydration and subsequent hydrogenation was converted to 4,5-diphenyl-2-dimethylaminopentane (XI). The same compound was obtained by heating (III) with potassium hydroxide in triethyleneglycol. It is not unlikely, therefore, that all the crystalline isomers obtained in this investigation, correspond to formula I and not to Ia.



X



XI

Additional evidence is made available by a study of the ultraviolet absorption of the substance concerned. Strait, Kumler, Sah, Alpen, and Chang (12) have recently reported that amidone (I, R = H) has three bands at 2600 Å, at 3000 Å and below 2600 Å, whilst isoamidone (Ia, R = H) has only one band, near 2600 Å, attributed to phenyl absorption. It is unlikely that the explanation given by the authors, that in amidone the two phenyl groups are not linked to the same carbon atom, is correct (the above discussed degradation methods

[2] While this material was in press, a paper by Bockmühl and Erhart (11), reporting a somewhat similar method of synthesis, came to our attention.

appear to preclude this possibility)—but the observation in itself provides an empirical tool capable of differentiating between the isomers (I) and (Ia). Fig. 1 shows the absorption spectrum of the hydrochloride of amidone (I,

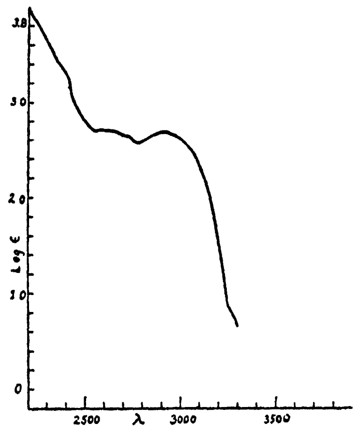


FIG. 1

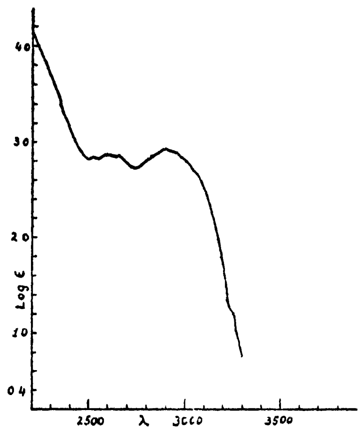


FIG. 2

FIG. 1. 2-DIMETHYLAMINO-4,4-DIPHENYL-5-HEPTANONE HYDROCHLORIDE (AMIDONE) (I, R = H), IN WATER

FIG. 2. 2-DIMETHYLAMINO-4-PHENYL-4-(p-TOLYL)-5-HEPTANONE HYDROCHLORIDE (I, R = CH_3), IN WATER

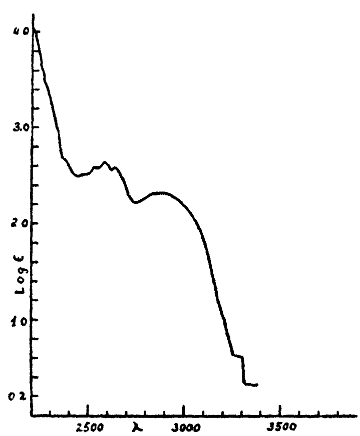


FIG. 3

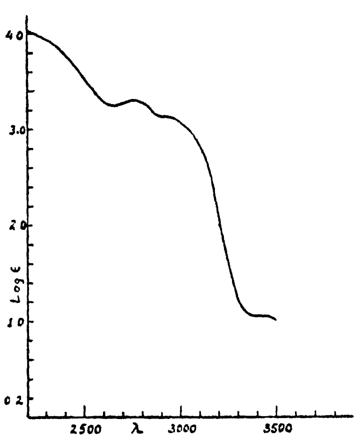


FIG. 4

FIG. 3. 2-DIMETHYLAMINO-4-PHENYL-5-BENZYL-5-HEPTANONE HYDROCHLORIDE (III), IN WATER

FIG. 4. 2-DIMETHYLAMINO-4-PHENYL-4-(p-METHOXYPHENYL)-5-HEPTANONE HYDROCHLORIDE (I, R = OCH_3), IN WATER

R = H) which is generally in agreement with the indications given by Strait and co-workers (12), and the spectra of the hydrochlorides of the tolyl compound (Fig. 2) and of the benzyl analog (Fig. 3) respectively are so similar to that of the parent substance that formulae (I, R = CH_3) and (III) appear

justified on spectro-analytical grounds, too. Also the methoxy-hydrochloride (Fig. 4) has a similar spectrum, so that it appears warranted to assign it formula (I, R = OCH_3). In the spectrum of the hydrochloride of the fluorene analog, too, (Fig. 5) the unexpected band at 3000 Å is present, which is an argument in favor of formula (II). It is interesting to note that the free base of (II) has practically the same spectrum as its hydrochloride (Fig. 6). Of course, in the fluorene compound one has to ascribe the very intense broad band at about 2650 Å to the absorption by the fluorene chromophor (13, 14, 15).

A detailed report on the physiological properties of the new compounds will be published elsewhere. An investigation of the fluorene derivative (II)

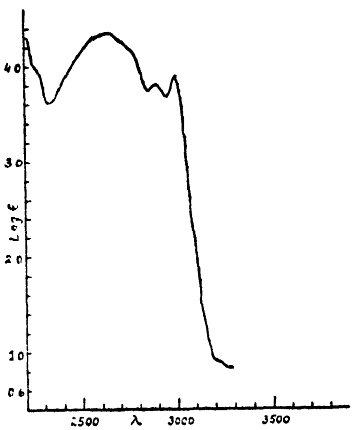


FIG. 5

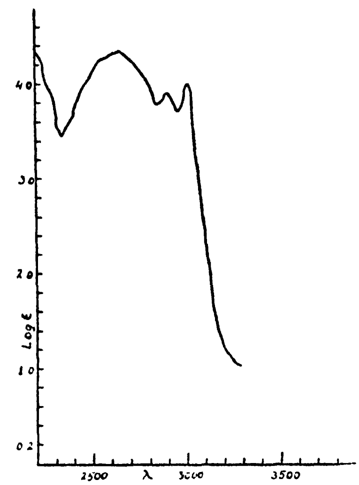


FIG. 6

FIG. 5. 9-(β-DIMETHYLAMINOPROPYL)-9-PROPIONYLFLUORENE HYDROCHLORIDE (II), IN WATER

FIG. 6. 9-(β-DIMETHYLAMINOPROPYL)-9-PROPIONYLFLUORENE (II), IN ALCOHOL

has been carried out in the Pharmacological Laboratories of Messrs. Geigy, Basle (Switzerland) through the courtesy of Dr. Krebser. The result was as follows: In doses of 0.5–5 mg./kg., the substance has a slight analgetic action, whilst amidone exhibits a strong analgetic effect in doses of 1.5 mg./kg. With 10 mg./kg. of the substance (II), tonic-clonic convulsions were observed (in rabbits). The average lethal dose was 62 mg./kg. (for amidone 17.5 mg./kg.) (intravenous injection in mice). The substance has also a spasmolytic effect, approximately of the same order as papaverine hydrochloride.

The help of Dr. Y. Hirshberg in determining the absorption spectra is gratefully acknowledged.

EXPERIMENTAL

The *diarylacetonitriles* were prepared from bromobenzyl cyanide by the Friedel-Crafts reaction. The method has been improved so as to give better yields, even of the parent substance, *diphenylacetonitrile*, which is thus obtained in a yield of 74% [50–51% according to Schultz, Robb, and Sprague (4)]. At 105–110°, bromine (17 cc.) was added to 35 g. of pure

(chlorine-free) benzyl cyanide with stirring over a period of thirty minutes. The heating was continued for another thirty minutes and the crude bromobenzyl cyanide was dissolved in 150 cc. of benzene. To this solution, 42 g. of powdered aluminum chloride was added within twenty to thirty minutes in portions of such size that the temperature rose to 45–50°. The reaction mixture was then heated for one hour at 60–65°, most of the benzene distilled off (maximum bath temperature 125°), and the hot residue treated with a mixture of 400 cc. of water, 400 g. of ice, and 20 cc. of hydrochloric acid. The resulting product was distilled with steam for twenty minutes and the reddish oil (which solidified upon cooling) redissolved in benzene. After washing with water and drying, the solvent was removed *in vacuo* and the diphenylacetonitrile purified by distillation under 0.2 mm. pressure; b.p. 121–125°, yield, 49 g. Crystallization from 1.2 parts of ethyl alcohol raised the m.p. from 67–69° to 75°; yield 43 g. (74%).

Phenyl-(p-tolyl)acetonitrile, prepared analogously, was an easily crystallizable oil, b.p. 164–170°/4 mm., m.p. 61°, after recrystallization from a small amount of ethyl alcohol; yield 65%. It has been synthesized before by a different method by Michael and Jeanprêtre (16, 17), who report b.p. about 240°/40 mm.; m.p. 61°.

Phenyl-(p-methoxyphenyl)acetonitrile. In its preparation, benzene was replaced by a solution of the theoretical quantity of anisole in three times its volume of nitrobenzene. Before decomposition, the reaction mixture was heated for one hour at 100–110°; b.p. 155–165°/2 mm ; yield 32%.

Phenyl-(p-bromophenyl)acetonitrile. Bromobenzyl cyanide was mixed with three times the theoretical quantity of bromobenzene and the aluminum chloride added. Reaction set in when the mixture was heated for a short while at 50°; it was completed at 100° (one hour). The oily product (b.p. 172–176°/0.8 mm.) crystallized; from ethyl alcohol clusters of needles, m.p. 82–83°; yield 80%.

Anal. Calc'd for $C_{14}H_{10}BrN$: C, 61.7; H, 3.7; N, 5.2.

Found: C, 61.5; H, 4.0; N, 5.2.

9-Cyanofluorene was most conveniently prepared according to Wislicenus and Russ (18) from formylfluorene oxime and thionyl chloride.

Phenylbenzylacetonitrile was obtained in 32% yield, when 38 g. of benzyl chloride was added, within forty-five minutes, to a mixture of benzyl cyanide (40 g.) and sodium butoxide (7 g. of sodium in 150 cc. of butanol) and the mixture was refluxed for four hours. Steam-distillation and vacuum-distillation of the residue, which was extracted previously with benzene, gave 23 g. of the desired nitrile, b.p. 158–170°/0 6 mm. The nitrile solidified spontaneously, and was recrystallized from alcohol; needles of m.p. 58° (19).

Whilst *2-dimethylamino-1-chloropropane* was prepared in the customary manner by reduction of ethyl β-dimethylaminopropionate to 2-dimethylamino-1-propanol and treatment of the latter with thionyl chloride in chloroform, an improved method was worked out for the preparation of *1-dimethylamino-2-chloropropane in toluene solution:* A mixture of 65 g. of dimethylamine, 65 g. of 1-chloro-2-propanol, and 90 g. of toluene was prepared at 5° and heated for ten hours in an autoclave at 95–100°. The crystals were filtered, washed with 250 cc. of toluene, and the combined toluene solutions added, with stirring, to a solution of 165 g. of thionyl chloride in 400 cc. of toluene, the temperature being kept at 10–15°. The reaction was complete after the resulting mass had been heated for six hours at 100°. The hydrochloride was washed with toluene; yield 90 g. (83%, calculated on the basis of chloropropanol). The product was dissolved in 90 cc. of water, and after addition of 125 cc. of toluene, was treated at 0° with 100 cc. of 50% potassium carbonate solution. The toluene solution was separated and the aqueous layer extracted with 75 cc. of toluene. The combined extracts were washed with 10 cc. of ice-water, twice with 10 cc. of saturated sodium chloride solution, and dried with sodium sulfate. To remove the last traces of water, 20 cc. of the filtered solution were distilled off and discarded. The solution contained approximately 56 g. of 1-dimethylamino-2-chloropropane.[3]

[3] For analysis, 10 g. of the solution is shaken with an excess of *N* hydrochloric acid and subsequently with water; the combined aqueous extracts are titrated.

9-(β-Dimethylaminopropyl)-9-cyanofluorene. At 45°, the suspension of 4.4 g. of sodamide in 75 cc. of toluene, containing 12 g. of 1-dimethylamino-2-chloropropane was treated, with stirring, with a solution of 19 g. of 9-cyanofluorene in 180 cc. of toluene, the temperature being kept at 50°. After heating for one hour at 55–60°, the temperature was raised slowly and the mixture refluxed for 75 minutes. After cooling and washing with water, the desired nitrile was extracted from the toluene layer with an excess of 15% hydrochloric acid, the aqueous solution washed once with toluene and made alkaline with an excess of 20% sodium hydroxide solution. The thick, yellow oil which separated was taken up with ether and the ethereal solution washed, dried, and distilled. Pale yellow, viscous oil, b p. 168–170°/0.3 mm.; yield 21 g. (76%).

Anal. Calc'd for $C_{19}H_{20}N_2$: C, 82.6; H, 7.2; N, 10.2.

Found: C, 82.2; H, 7 1; N, 10.5.

In this and the other cases, summarized in Table I, the same product was obtained whether 1-dimethylamino-2-chloropropane or 2-dimethylamino-1-chloropropane was employed.

Amidones. The nitriles, prepared as described above, were directly treated with ethylmagnesium bromide and the resulting ketimines hydrolyzed in the manner outlined for the fluorene derivative (II).

TABLE I

BASIC NITRILES

MIXTURE OF	B.P., °C /MM.	YIELD, %	FORMULA	ANALYSIS Calc'd C	H	N	Found C	H	N
VII and VIIa, R = OCH_3	162–168/0.1	44	$C_{20}H_{24}N_2O$	77.9	7.8	9.1	78.0	7.7	9.2
VII and VIIa, R = CH_3.	148–155/0.1	69	$C_{20}H_{24}N_2$	82.2	8.2	9.5	82.0	8.5	9.1
VII and VIIa, R = Br . . .	162–170/0 05	74	$C_{19}H_{21}BrN_2$	63.9	5 9	7 8	64 1	6.0	7.8
Phenylbenzyl-(β-dimethylaminopropyl)- and -(β-dimethylaminoisopropyl)-acetonitrile	148–155/0.1	70	$C_{20}H_{24}N_2$	82.2	8.2	9.5	82.3	8.1	9.5

9-(β-Dimethylaminopropyl)-9-propionylfluorene (II). To a boiling solution, prepared from 6.5 g. of magnesium and 26 cc. of ethyl bromide in 60 cc. of ether, 20 g. of 9-(β-dimethylaminopropyl)-9-cyanofluorene in 100 cc of benzene was added, and most of the ether was distilled off simultaneously. The reaction mixture was then refluxed for 10 hours, decomposed with an ice-cold ammonium chloride solution, and extracted with 30 cc. of cold, 25% sulfuric acid. The acid extract was washed once with benzene and after the further addition of 50 cc. of sulfuric acid, heated at 100° for 90 minutes. After cooling, the solution was made alkaline with 33% aqueous sodium hydroxide solution and the oil which separated was taken up in benzene, b.p. 152–158°/0.6 mm.; yield 14.5 g. (65%). The oil solidified upon standing; from 85% alcohol, m.p. 66–68°. The substance was characterized as the *hydrochloride*, which was obtained in 86% yield when the base in isopropanol was treated with an isopropanolic hydrogen chloride solution. After recrystallization from the same solvent, it had m.p. 262–264°.

Anal. Calc'd for $C_{21}H_{26}ClNO$: N, 4.1. Found: N, 4.5.

The other basic ketones were prepared analogously; as already pointed out, the hydrochlorides corresponding to formula (I) were obtained by adding only half of the theoretical quantity of isopropanolic hydrogen chloride solution to the solution of the basic ketones in isopropyl alcohol and precipitating with ether. When the filtrates were treated with isopropanolic hydrogen chloride, no precipitate was obtained, and evaporation of the

solutions gave reddish, hygroscopic powders, from which no defined substance could be isolated. The crystalline hydrochlorides were converted into the picrates with sodium picrate in alcohol.

The mixture of the basic ketones (III and IIIa), which was obtained in 75% yield, boiled at 174–178°/0.2 mm.; it gave the correct analytical figures.

Anal. Calc'd for $C_{22}H_{29}NO$: C, 81.7; H, 9.0; N, 4.3.

Found: C, 82.0; H, 9.2; N, 4.5.

The *hydrochloride*, prepared in the manner indicated above, was an oil which had to be triturated with ether at 0° for several days, before crystallizing. Recrystallization from butyl acetate gave crystals of m.p. 100–103° which apparently contained one mole of water of crystallization.

Anal. Calc'd for $C_{22}H_{30}ClNO \cdot H_2O$: C, 70.0; H, 8.0.

Found: C, 70.3; H, 8.5.

TABLE II

BASIC KETONES (I)

MIXTURES OF	B.P., °C./MM.	YIELD, %	HYDROCHLORIDE OF	RECRYSTALLIZED FROM	M.P., °C.	ANALYSIS Calc'd C	Calc'd H	Calc'd N	Found C	Found H	Found N
I, Ia (R = CH_3)	175–180/2	82	I, $C_{22}H_{29}NO \cdot HCl$	butyl acetate	202–204	73.5	8.4	3.9	73.7	8.6	4.2
I, Ia (R = OCH_3)	160–163/0.1	60	I, $C_{22}H_{29}NO_2 \cdot HCl$	butyl acetate	162–163	70.4	8.0	3.7	70.4	8.1	4.0
I, Ia (R = Br)	175–180/0.1	80	I, $C_{21}H_{26}BrNO \cdot HCl$	butyl acetate	205–207	59.4	6.4	3.3	58.9	6.7	3.4

PICRATE, M.P., °C.	FORMULA	ANALYSIS Calculated C	Calculated H	Calculated N	Found C	Found H	Found N
138–140	$C_{28}H_{32}N_4O_8$; from ethanol	60.9	5.8	10.1	60.5	5.8	10.0
178–179	$C_{28}H_{32}N_4O_9$	59.1	5.6	9.9	58.7	5.6	9.8
153–154	$C_{27}H_{29}BrN_4O_8$; from ethanol	52.5	4.6	9.1	52.0	4.7	9.4

Drying at 90–95° (*in vacuo*) gave the anhydrous hydrochloride, which melted at 145–147°. The *picrate* had m.p. 164–166° after several recrystallizations from ethyl alcohol and butyl acetate. From the mother liquors, a small amount of a second [isomeric (IIIa)?] *picrate*, m.p. 152°, could be isolated.

Anal. Calc'd for $C_{28}H_{32}N_4O_8$: C, 60.9; H, 5.8; N, 10.1.

Found: C, 60.5; H, 5.8; N, 10.0.

From the picrate of m.p. 164–166°, the basic ketone (III) could be isolated in pure form, by treatment with sodium hydroxide solution. Recrystallization from 90% methanol gave well-shaped crystals of m.p. 67–68°.

Anal. Calc'd for $C_{22}H_{29}NO$: N, 4.3. Found: N, 4.7.

β-Dimethylaminobutyrophenone (VIII) (11). A mixture of 42 g. of propenylphenylketone (20) and 60 g. of toluene was cooled at 5–10° and after the addition of 30 g. of dimethylamine, was heated at 60° for eighteen hours in an autoclave. The solvent was removed *in vacuo* and the residue heated at 70° for two hours. The crude product (45 g.) was used for the reaction with Grignard compounds, as (VIII) tends to decompose into the components

during all attempts at purification. Its *picrate*, from ethyl alcohol, m.p. 122–123°, could be isolated in a fairly pure state.

Anal. Calc'd for $C_{18}H_{20}N_4O_8$: C, 51.4; H, 4.8; N, 13.3.
Found: C, 52.4; H, 5.1; N, 12.7.

1,1-Diphenyl-3-dimethylamino-1-butanol (11). To a Grignard solution, prepared from 1.2 g. of magnesium and 8 g. of bromobenzene, there was added, with cooling, an ethereal solution of 9.5 g. of the crude amino ketone. After refluxing the mixture for thirty minutes, it was decomposed with ice and ammonium chloride, and the ethereal solution extracted with dilute hydrochloric acid from which the basic alcohol was liberated by treatment with aqueous sodium hydroxide solution and ether. The oily product crystallized upon standing; from ethanol, m.p. 120–122°; yield 0.8 g. *Picrate*, from ethyl alcohol, m.p. 160–162°.

Anal. Calc'd for $C_{24}H_{26}N_4O_8$: N, 11.2. Found: N, 11.1.

The *carbinol* could not be reduced to 3-dimethylamino-1,1-diphenylbutane by catalytic hydrogenation in presence of perchloric acid (21), using palladium or Raney nickel as catalyst.

1,1-Diphenyl-3-dimethylamino-1-butene (IX). The above carbinol (1 g.) was heated with potassium hydrogen sulfate (2 g.) at 150–160° for ninety minutes. The reaction product was dissolved in water and the solution treated with sodium hydroxide solution and ether. The oily product was characterized as its *picrate*, m.p. 195–196°.

Anal. Calc'd for $C_{24}H_{24}N_4O_7$: N, 11.7. Found: N, 11.5.

1,1-Diphenyl-3-dimethylaminobutane. The olefin (IX) was hydrogenated in ethanolic solution at room temperature and atmospheric pressure, using nickel as catalyst. The theoretical amount of hydrogen was absorbed in six hours. The *picrate* obtained from the filtered solution had m.p. 138–140° and was identical with the product according to May and Mosettig (10).

4,5-Diphenyl-2-dimethylamino-4-pentanol (X). The reaction between β-dimethylaminobutyrophenone (VIII) and benzylmagnesium chloride was carried out as above, but at 0°. After two hours' standing at room temperature, the product was decomposed with ice and ammonium chloride and the ethereal layer extracted with dilute acetic acid. The aqueous solution was made alkaline with potassium carbonate solution and extracted with benzene. The amino alcohol crystallized spontaneously; from ethyl alcohol, m.p. 94–95°; yield, 28%. *Picrate*, from ethyl alcohol, m.p. 135–137°.

Anal. Calc'd for $C_{25}H_{28}N_4O_8$: C, 58.6; H, 5.5; N, 10.95.
Found: C, 58.8; H, 6.1; N, 11.7.

4,5-Diphenyl-2-dimethylaminopentane (XI). (a) The amino alcohol (X) was dehydrated with potassium hydrogen sulfate, as described above, and the crude dehydration product[4] hydrogenated in ethyl alcohol with a Raney nickel catalyst. The hydrogenation required thirty minutes. The filtered solution was treated with picric acid and the *picrate* recrystallized from a mixture of ethyl alcohol and acetone; m.p. 168–170°.

Anal. Calc'd for $C_{25}H_{28}N_4O_7$: C, 60.5; H, 5.65; N, 11.3.
Found: C, 61.10; H, 6.3; N, 11.7.

(b) The ketone (III) was degraded in the following manner: One gram of the pure base (m.p. 67–68°), 0.8 g. of potassium hydroxide, and 5 cc. of triethyleneglycol were heated for four hours at 220–225°. The reaction product was cooled and treated with ether and water, and the residue of the ethereal layer taken up with 20 cc. of alcoholic picric acid solution; then 20 cc. of water was added. Three crystallizations of the precipitate from an alcohol-acetone mixture (10:1) gave the *picrate* of m.p. 168–170° which was not depressed by admixture of the synthetic substance.

SUMMARY

The 4-methoxy, 4-bromo, and 4-methyl derivatives of amidone were synthesized in the manner used in the synthesis of the parent substance. Likewise,

[4] No attempt was made to purify the dehydration product or to determine whether the double bond was situated in 4,5 or in 3,4.

9-(β-dimethylaminopropyl)-9-propionylfluorene (II) and 4,5-diphenyl-4-(β-dimethylaminopropyl)-3-pentanone (III) were synthesized.

With the exception of the fluorene compound (II), mixtures of isomers, corresponding in structure to amidone (I, R = H), and isoamidone (Ia, R = H), were obtained, from which one isomer could be isolated in pure form. It has been proven or at least made probable that these crystalline compounds are analogous to amidone and not to the isocompound. For the proof of these structures, the ultraviolet absorption spectra of the new substances have been utilized.

The pharmacological properties of the fluorene derivative (II) are reported.

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[Contribution from the Department of Chemistry, Columbia University]

CASHEW NUT SHELL LIQUID. V. THE MONOPHENOLIC FRACTION. A SYNTHETIC INVESTIGATION OF THE GEOMETRICAL CONFIGURATION OF THE MONOÖLEFINIC COMPONENT[1]

MEYER SLETZINGER[2] and CHARLES R. DAWSON

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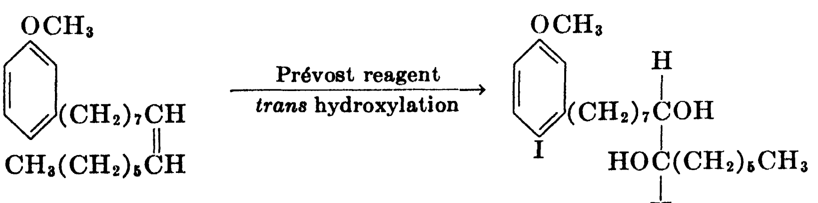
In a previous communication from these laboratories (1), evidence establishing the heterogeneous olefinic nature of the monophenolic component of commercial cashew nut shell liquid was reported. The monophenol was shown to be a mixture of at least two olefinic components; one a monoölefin and the other a diolefin. It must also be presumed that higher olefinic components were also present in order to account for the unsaturation (equivalent to about two olefinic bonds) of the freshly distilled monophenol. The structure of the monoölefinic component was established as that of a 3-(pentadecenyl-8′)phenol.

Two geometrical isomers of 3-(pentadecenyl-8′)phenol are possible, (see methyl ethers A and B), and it was the purpose of the present investigation to establish which of these configurations is that of the natural occurring monoolefin.

As the first step toward this objective, the *cis* methyl ether (A) was synthesized employing a method (2) which had previously been developed for the purpose. Because of their liquid nature, it was not advantageous to attempt a comparison of the synthetic *cis* isomer directly with the methyl ether of the natural occurring monoölefinic phenol. Consequently, both were converted into their corresponding crystalline glycols by means of the Prévost reagent, silver iodobenzoate (3). The hydroxylation of an olefinic bond by this reagent is known to be stereospecific and result in a *trans* hydroxylation (3b, 4).[3] Thus the spatial configuration of the iodinated glycol[4] (C) obtained from the synthetic *cis* olefin (A) is deducible *i.e.*,



(A) *Cis* (C)

[1] For the fourth article in this series, see Sletzinger and Dawson, *J. Org. Chem.*, **14**, 670 (1949).

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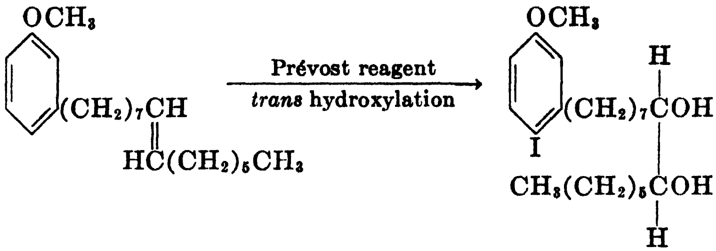
[3] The observation (4) that the interaction of silver iodobenzoate with an ester of oleic acid (*cis* double bond) yields upon hydrolysis exclusively the low-melting form of 9,10-dihydroxystearic acid has been confirmed in these laboratories.

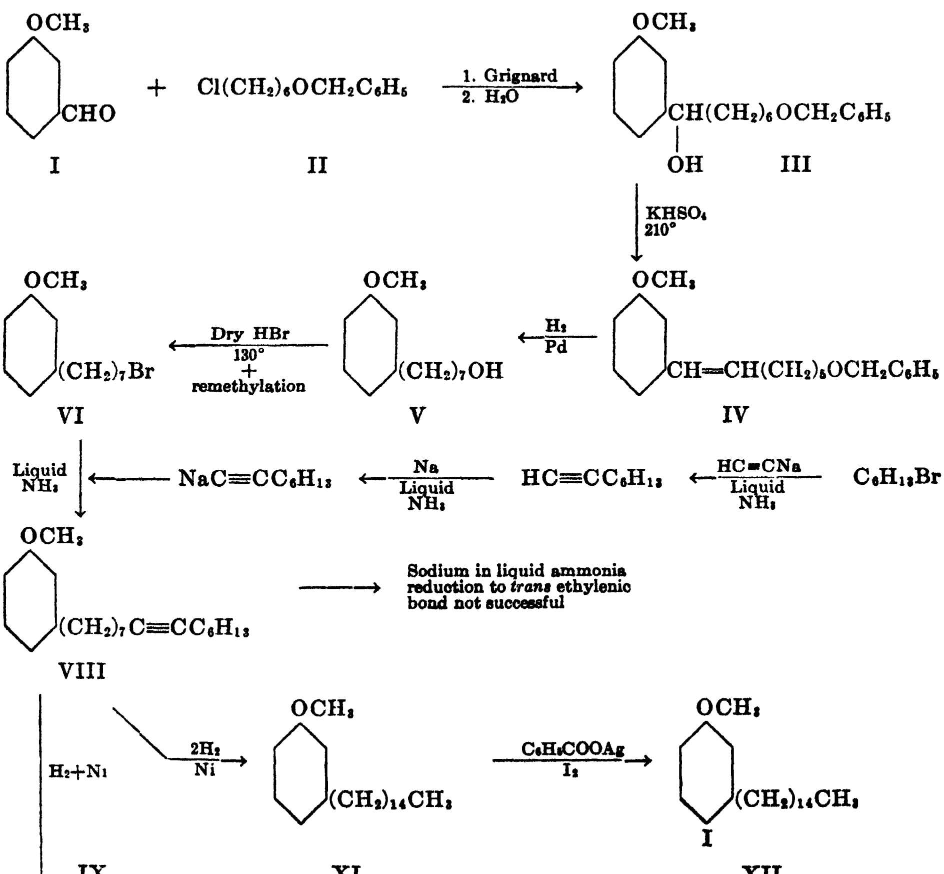
[4] The hydroxylation of olefinic phenolethers by means of silver iodobenzoate results in the simultaneous iodination of the ring (1).

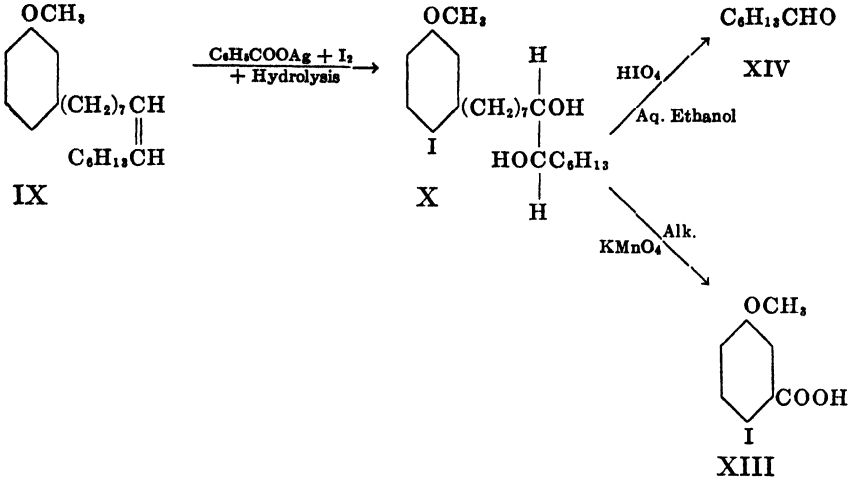
Furthermore, it can be reasoned that the configuration of the glycol obtained from the natural occurring monoölefin must be either that of (C) or the diastereoisomer (D).



(B) *trans* (D)

Accordingly, when it was found that the hydroxylation of the synthetic *cis* olefin (A) resulted in an iodinated glycol having different physical properties than that obtained by similarly hydroxylating the natural occurring monoölefin, the geometric structure of the latter was established as that of the *trans* isomer (B).





The desired *cis* olefin (IX) was synthesized starting with *m*-methoxybenzaldehyde (I), using the sequence of reactions outlined on the Flow Sheet. The experimental conditions for the synthesis, which involved as its essential feature the stereospecific reduction of an acetylenic compound (VIII), had been previously developed by Wasserman and Dawson (2) in connection with their investigations of Poison Ivy "Urushiol." However, in the present investigation certain modifications in procedure were introduced which resulted in decided improvements of yield. Thus it was found advantageous to convert the alkyl halide (VI) into the desired acetylene (VIII) by a one-step process involving the sodium salt of octyne-1 (VII) in liquid ammonia, rather than by sodium acetylide and then heptyl bromide as Wasserman and Dawson reported.

Repeated attempts to reduce the acetylenic compound (VIII) to a *trans* olefin with sodium in liquid ammonia (2) at atmospheric pressure, and also at higher pressures in a steel bomb, were not successful. The 3-(pentadecynyl-8′)anisole (VIII) was found to be unexpectedly resistant to the sodium liquid ammonia reduction, and no appreciable yield of olefin was obtained, judging from subsequent quantative hydrogenation data.

The *cis* olefin (IX) was readily obtained by catalytic reduction of the acetylenic compound (VIII) using Raney nickel. Previous investigations (5) established that Raney nickel is stereospecific in catalyzing the hydrogenation of acetylenic bonds. The reduction was allowed to proceed to about 15% in excess of 1 mole equivalent of hydrogen in order to insure that no acetylenic compound remained. The hydrogenated product was then treated with silver iodobenzoate and the resulting benzoates were hydrolyzed. The hydrolysis mixture yielded two crystalline products. One of these, 4-iodo-3-pentadecylanisole (XII), was obtained as the result of the excess hydrogenation. The other product, the expected iodinated glycol (X), melted at 73–74°.

It had been previously established (1) that the action of the Prévost reagent on the methylated monophenolic fraction obtained by vacuum distillation of commercial cashew nut shell liquid resulted in a crystalline iodinated mono-

glycol melting at 92–93°, *i.e.*, nineteen degrees higher than the monoglycol (X) obtained from the synthetic *cis* olefin (IX). The diastereoisomeric character of these two glycols was confirmed by analysis, melting point determination, and the following oxidation experiments. The lower melting glycol (X) (synthetic) on oxidative cleavage with periodic acid yielded *n*-heptaldehyde (XIV) just as previously reported (1) for the glycol derived from the natural oil. Furthermore, oxidation of (X) with alkaline permanganate yielded the same iodomethoxybenzoic acid (XIII).

On the basis of the above results, it may be concluded that the higher-melting monoglycol (92–93°) has the configuration (D), and accordingly the mono-olefinic component of the monophenolic fraction of cashew nut shell liquid is a *trans* olefin (see methyl ether, B).

It is clear that the above conclusions are based primarily on the acceptance of a *cis* configuration for the synthetic olefin and a stereospecific hydroxylation by the Prévost reagent. As pointed out earlier, sufficient grounds for such basic assumptions have been provided by previous investigations of the Raney nickel hydrogenation of acetylenic bonds (5) and the action of silver iodobenzoate on olefins (3b, 4). Furthermore, the above conclusions are in line with the fact that a glycol which results from the *cis* hydroxylation of a *cis* double bond or the *trans* hydroxylation of a *trans* double bond is ordinarily higher melting than the glycol which results from the *trans* hydroxylation of a *cis* double bond or the *cis* hydroxylation of a *trans* double bond. Evidence for this is obtained from the tartaric acids, the 2,3-butylene glycols, and the 9,10-dihydroxystearic acids.

EXPERIMENTAL

m-Methoxybenzaldehyde (I). This aldehyde was prepared according to the directions given in Organic Syntheses (6).

1-Chloro-6-benzyloxyhexane (II). This compound was prepared using the directions given by Wasserman and Dawson (2).

3-(7′-Benzyloxyheptanol-1′)anisole (III). To a two-liter three-necked flask equipped with a dropping-funnel, bulb condenser, and sealed stirrer was added 22 g. of magnesium turnings, 85 cc. of sodium-dried ether, 0.5 g. of methyl iodide, and a crystal of iodine. After the methylmagnesium iodide had formed, a solution of 208 g. of II dissolved in 200 cc. of dry ether was added through the dropping-funnel at such a rate as to keep the reaction going vigorously. After four hours the addition was complete and the black solution was refluxed for an additional hour. A small amount of magnesium remained unreacted. The flask was cooled in an ice-bath and 100 g. of *m*-methoxybenzaldehyde (I) dissolved in 350 cc. of dry ether was slowly added with stirring. The mixture turned white on addition of the aldehyde but cleared on standing overnight. It was hydrolyzed with 600 cc. of 6 *N* sulfuric acid, the ether layer was washed with 10% sodium carbonate, and then with water. It was evaporated, and the remaining liquid dried by the addition of benzene and distillation. A yellow oil remained which was not further purified.

3-(7′-Benzyloxyheptenyl-1′)anisole (IV). The crude secondary alcohol (III) was placed in a 500-cc. flask equipped with a Vigreux column. Five grams of fused potassium bisulfate was added and the flask was heated slowly to 210°. The formation of water was indicated by violent spattering. After 15 minutes the flask was cooled and water was removed by distilling some xylene from the mixture. After filtering from the salt, the brown filtrate was distilled using a six-inch helices-packed column which was electrically heated. The main

fraction distilled at 205–208°/1 mm. (bath temp. 250–280°) and yielded 154 g. (68%) of colorless liquid; n_D^{25} 1.5547.

Anal. Calc'd for $C_{21}H_{26}O_2$: C, 81.29; H, 8.39.

Found: C, 81.10; H, 8.36.

3-(Heptanol-7')anisole (*V*). A 60-g. sample (0.194 mole) of IV with 0.5 g. of palladium black and 120 cc. of glacial acetic acid was reduced at atmospheric pressure in an Adams shaker for five hours. The theoretical amount of hydrogen (0.387 mole) was absorbed. The catalyst was removed and washed with acetic acid. The solvent was removed *in vacuo* with the toluene formed. The remaining liquid was fractionated with a 6-inch helices-packed electrically-heated column. The main fraction boiled between 148–154°/1.5 mm. (bath temperature, 200°). The yield was 40 g. of clear colorless liquid. This material was used in the next step without further purification.

3-(7'-Bromoheptyl)anisole (*VI*). A 32-g. sample of V was placed in a 100-cc. flask and dry hydrobromic acid was bubbled through for 9 hours at 130–135°. A water layer soon formed and settled to the bottom. The flask was cooled and the contents poured into a separatory funnel containing water. The mixture was extracted with benzene and washed again with water. The benzene solution was dried over magnesium sulfate, distilled, and the red residue was remethylated at the phenolic hydroxyl groups liberated during the esterification. Dimethyl sulfate (11.2 grams), 100 cc. of methanol, and 20 cc. of dioxane was added to the flask. A solution of 7 g. of KOH in 30 cc. of methanol was then added rapidly, by means of a dropping-funnel with constant stirring. The temperature rose to 50°. Stirring was continued until the reaction was acidic to Alkacid paper. At this point 6 g. of dimethyl sulfate was added to the flask and 3.5 g. of KOH in 15 cc. of methanol as above. The solution was refluxed for 15 minutes, when it was acidic again. The reaction mixture was then added to two liters of water and extracted with benzene. The brownish benzene layer was washed with sodium bicarbonate solution, dried over magnesium sulfate, filtered, and evaporated *in vacuo* to a reddish oil. This was then fractionated. The fraction boiling at 159°/1 mm. (bath temperature 198°) yielded 28 g. (63%) of colorless clear liquid, heavier than water; n_D^{25} 1.5240.

Anal. Calc'd for $C_{17}H_{21}BrO$: C, 58.94; H, 7.37.

Found: C, 58.71; H, 7.66.

1-Octyne (*VII*). Into a three-necked flask containing 300 cc. of liquid ammonia and equipped with a stirrer and gas inlet-tube 17.6 g. of sodium was added in small strips while acetylene was simultaneously bubbled through the solution. The acetylene was obtained from a commercial source and was purified by passing it through a wash bottle of conc'd sulfuric acid, a Dry Ice-methanol bath, and finally a soda-lime drying tower. At no time was a great excess of sodium added. The acetylene was passed through the solution until the blue color was completely discharged and for an additional five minutes in order to insure the conversion to the monosodium acetylide.

A Dry Ice-methanol reflux condenser (cold finger) was then inserted into the apparatus and with stirring 63 g. of *n*-hexyl bromide was added by means of a dropping-funnel over the course of 1.5 hours. The volume of the solution was maintained at 300 cc. by the addition of liquid ammonia when necessary. After all the bromide had been added, stirring and reflux was maintained for an additional two hours. At this point the Dry Ice condenser was removed, and the ammonia was allowed to evaporate, leaving a white solid residue in the flask. This was treated with 50 cc. of 5% ammonium chloride solution, whereupon two layers appeared; an upper yellow organic layer and the bottom water layer. The mixture was extracted with ether and the ether solution washed with dilute hydrochloric acid and water, and dried over magnesium sulfate. The solvent was removed by fractionation through a 10-in. Widmer column. The product was distilled using a helices-packed column; it boiled at 125–126°/759 mm. Yield, 50 g. of octyne-1 (59.5%).

3-(Pentadecynyl-8')anisole (*VIII*). Into a 500-cc. three-necked flask equipped with a stirrer and containing 100 cc. of liquid ammonia, was added 0.2 g. of hydrated ferric nitrate. To this solution 0.5 g. of sodium was added with stirring. The solution at first turned blue,

but after 15 minutes became grayish, indicating the formation of sodamide. A total of 1.5 g. of sodium was added in small strips with stirring over thirty minutes. When all the sodium was converted to sodamide, as indicated by the disappearance of the blue color, the volume of ammonia was increased to 300 cc. and a Dry Ice-methanol condenser was inserted into the apparatus.

A 7.5-gram sample of 1-octyne was added dropwise over a period of one hour with stirring. A white solid deposited. Throughout the course of the reaction the volume of ammonia was maintained at 300 cc. by the addition of liquid ammonia. After the formation of sodium octyne, the addition of 10 g. of VI dissolved in 15 cc. of dry ether was begun over a period of three hours with stirring and reflux. At the end of this time the reflux was discontinued but stirring was continued without reflux until all the ammonia had evaporated, leaving a grayish solid. The solid was decomposed with 150 cc. of 5% ammonium chloride solution and the organic layer extracted with ether. The ether extract was washed with 30 cc. of 10% hydrochloric acid and water, and dried over magnesium sulfate. It was evaporated to an oil, which was fractionated using a 15-cc. Spitzkolben, b.p. 186–188°/0.8 mm. (bath temp., 230°). The distillate was slightly yellow in color and weighed 4.8 g. (43%); n_D^{25} 1.4958.

Anal. Calc'd for $C_{22}H_{34}O$: C, 84.08; H, 10.82.

Found: C, 83.93; H, 10.96.

3-Pentadecylanisole (XI). A 0.4995-gram sample of VIII (0.00156 mole) was reduced in 25 cc. of ethanol using Raney nickel as a catalyst. The reduction was complete in one hour and resulted in the absorption of 0.00312 mole of hydrogen, thereby confirming the existence of an acetylenic bond in VIII. After filtering the filtrate was concentrated to 2 cc. and cooled. The result was a quantitative yield of hair-like needles melting at 29–30°. A mixed melting point with a sample of the 3-pentadecylanisole (m.p. 29–30°) derived from natural sources showed no depression, thereby confirming the straight chain character of the side chain of VIII.

Cis-3-(pentadecenyl-8')anisole (IX). A 4.7-gram sample of the acetylenic compound VIII was hydrogenated in 75 cc. of ethanol using Raney nickel as a catalyst at 30° and 755 mm. pressure. Under these conditions the theoretical amount of hydrogen required for reduction to the olefinic stage is 380 cc. To insure that no acetylenic compound would remain and thereby complicate subsequent studies of the application of the Prévost reagent to this synthetic *cis*-olefin, the reduction was allowed to proceed until 427 cc. of hydrogen had been absorbed. The catalyst was removed and the alcohol distilled. The residual oil was fractionated; the main fraction boiled at 186–189°/0.8 mm.; yield, 4.2 g. (87%) of a clear colorless liquid.

3-(8', 9'-Dihydroxypentadecyl)-4-iodoanisole (X). A 2.0-gram sample of the *cis*-olefin prepared as described above was added to a solution of 3.26 g. of I_2 in 100 cc. of thiophene-free, anhydrous benzene which contained 4.4 g. of silver benzoate in suspension. The mixture was refluxed for two hours. At the end of this time the iodine color had disappeared. The solution was cooled, filtered from the insoluble silver iodide, and evaporated on a steam-bath, *in vacuo*, to an oil. The oil was dissolved in 50 cc. of 80% ethanol containing 5 g. of KOH and refluxed with occasional stirring for three hours. A brownish solution resulted which was concentrated to a volume of about 5 cc. Then 50 cc. of water was added and the insoluble oil extracted with three 25-cc. portions of ether. The combined ether extracts were washed with water, dried over magnesium sulfate, and evaporated to an oil. The oil was taken up in 75 cc. of hot 95% ethanol and cooled. The crystalline product was recrystallized three times from 95% ethanol. The 1.0-gram yield of crystalline material melted at 43° and analyzed correctly for 4-iodo-3-pentadecylanisole (XII). It presumably resulted from the excess hydrogenation described above.

Anal. Calc'd for $C_{22}H_{37}IO$: C, 59.48; H, 8.3.

Found: C, 59.32; H, 8.35.

The ethanolic mother liquors from the above reaction were evaporated to dryness *in vacuo* and 75 cc. of hot methanol was added in order to dissolve all of the oil. The solution was slowly cooled in an ice-box overnight and the product was recrystallized three times

from Skellysolve B to give a crystalline solid of m.p. 73–74° (yield, 1.3 g.) which analyzed correctly for the iodomonoglycol (X).

Anal. Calc'd for $C_{22}H_{37}IO_3$: C, 55.34; H, 7.74.

Found: C, 55.46; H. 7.78.

Oxidation of X with periodic acid. A 1.0-gram sample of X was oxidized in aqueous methanol using the same procedure as described previously (1) for the oxidation of the iodomonoglycol obtained from the natural oil. A 400 mg. yield of the *2,4-dinitrophenylhydrazone* of *n-heptaldehyde* (XIV) proved that the ethylenic bond of IX had not migrated during the hydroxylation reaction. A mixed melting point with an authentic sample of the 2,4-dinitrophenylhydrazone of *n*-heptaldehyde (m.p. 106–107°) showed no depression.

Oxidation of X with alkaline permanganate. A 200-mg. sample of X was oxidized in 25 cc. of water containing 1.0 g. of $KMnO_4$ and 0.2 cc. of 0.2 *N* NaOH using the same procedure as previously described (1) for the oxidation of the iodomonoglycol obtained from the natural oil. The iodomethoxybenzoic acid (XIII) was isolated (30 mg., yield 23%) and melted at 136–137°. A mixed melting point with the acid obtained from the iodomonoglycol of natural origin (1) showed no depression.

ACKNOWLEDGMENT

The authors are indebted to the Irvington Varnish and Insulator Company of Irvington, New Jersey, for the supply of commercial cashew nut shell liquid, and for their helpful interest in this investigation. The authors also wish to thank Miss Lois May who carried out the microanalyses reported in this communication.

SUMMARY

The methyl ether of 3-(pentadecenyl-8′)phenol has been synthesized by a method which is believed to yield only the *cis* isomer. Treatment of this synthetic olefin with the Prévost reagent, silver iodobenzoate, yields on subsequent hydrolysis a crystalline iodomonoglycol melting at 73–74°.

Reaction of the Prévost reagent with the methylated monophenolic fraction of cashew nut shell liquid (either commercial or solvent extracted) results in an isomeric monoiodoglycol melting at 92–93°.

Both glycols have been shown by oxidative degradations to possess the structure of 3-(8′,9′-dihydroxypentadecyl)-4-iodoanisole.

On the basis of a *cis* configuration for the synthetic olefin, and a stereo specific hydroxylation by means of the Prévost reagent, it may be concluded that the monoölefinic component of the monophenolic fraction of cashew nut shell liquid possesses a *trans* ethylenic configuration.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

SYNTHESIS OF DIETHYL ARYLMALONATES FROM DIETHYL MESOXALATE

ARTHUR C. COPE AND LAMAR FIELD

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Diethyl arylmalonates are commonly prepared from ethyl arylacetates, either by condensation with diethyl oxalate followed by decarbonylation of the resulting oxaloesters (1, 2), or by condensation with diethyl carbonate (3, 4, 5). Some ethyl arylacetates can be obtained only by rather long routes, and in such cases a more direct synthesis of diethyl arylmalonates would be advantageous. This paper reports a synthesis of diethyl arylmalonates from diethyl aryltartronates, $ArC(OH)(COOC_2H_5)_2$, by treatment with thionyl chloride to form diethyl arylchloromalonates, followed by catalytic hydrogenation to replace the chlorine by hydrogen. This method should be useful in cases in which the diethyl aryltartaronates are more readily available than ethyl arylacetates.

A number of diethyl aryltartronates have been prepared by condensation of aromatic hydrocarbons or their derivatives with diethyl mesoxalate in the presence of acidic catalysts, such as sulfuric acid or stannic chloride (6, 7, 8, 9, 10, 11, 12).[1] This synthesis has proved to be very useful in a number of instances in which the aromatic compounds are reactive enough to condense with diethyl mesoxalate, and where the directive influence of substituents produces the desired orientation of the entering —$C(OH)(COOC_2H_5)_2$ group. This paper describes a new synthesis of diethyl aryltartronates, in which Grignard reagents are added selectively to the very reactive carbonyl group of diethyl mesoxalate at −70°.[2] It should be possible to extend this synthetic method to many of the aryl halides from which Grignard reagents can be prepared, and the method should be useful in some of the cases in which diethyl aryltartronates cannot be prepared by the condensation of aromatic compounds with diethyl mesoxalate.

In the synthesis of diethyl 9-phenanthrylmalonate (IV), 9-phenanthrylmagnesium bromide was added to diethyl mesoxalate at a reaction temperature of − 70° to −65°. Hydrolysis of the adduct gave diethyl 9-phenanthryltartronate (I) in 46% yield.

$$9\text{-}C_{14}H_9MgBr \;+\; CO(COOC_2H_5)_2 \xrightarrow{\text{(after hydrolysis)}}$$

$$\underset{\text{I}}{9\text{-}C_{14}H_9C(OH)(COOC_2H_5)_2} \xrightarrow{\text{KOH, then HCl}} \underset{\text{II}}{9\text{-}C_{14}H_9CH(OH)COOH}$$

[1] Diethyl diarylmalonates are formed from the same reactants in some cases under more strenuous conditions (13, 14).

[2] A reaction temperature of −70° was used because of the greater selectivity observed for the reaction of Grignard reagents with other polyfunctional compounds at low temperatures in certain instances, such as the preparation of ketones from Grignard reagents and acid anhydrides reported by Newman and Booth (15) and Newman and Smith (16).

The crystalline ester I was characterized by saponification and decarboxylation, which yielded 9-phenanthrylglycolic acid (II). Treatment of diethyl 9-phenanthryltartronate (I) with thionyl chloride and a small amount of pyridine gave diethyl 9-phenanthrylchloromalonate (III) in 84–95% yield. The chloroester III decomposed with evolution of hydrogen chloride at the melting point, which was somewhat erratic although the ester was analytically pure. Catalytic hydrogenation of III in the presence of palladium on Norit gave diethyl 9-phenanthrylmalonate (IV) in yields of 94–98%. IV was characterized by saponification and decarboxylation to 9-phenanthrylacetic acid (V), which was identified by m.p. and mixture m.p. with a known sample (17).[3]

$$\mathrm{I} \xrightarrow{SOCl_2} \underset{\mathrm{III}}{9\text{-}C_{14}H_9C(Cl)(COOC_2H_5)_2} \xrightarrow{H_2,\ Pd}$$

$$\underset{\mathrm{IV}}{9\text{-}C_{14}H_9CH(COOC_2H_5)_2} \xrightarrow{\text{KOH, then HCl}} \underset{\mathrm{V}}{9\text{-}C_{14}H_9CH_2COOH}$$

Diethyl α-naphthylmalonate was prepared by a sequence of reactions similar to the one outlined above, beginning with the addition of α-naphthylmagnesium bromide to diethyl mesoxalate. Diethyl α-naphthyltartronate was obtained as a sirup which failed to crystallize, but was characterized as a crystalline ester (prepared by reaction with benzoyl chloride), diethyl O-benzoyl-α-naphthyltartronate. The reaction of diethyl α-naphthyltartronate with thionyl chloride yielded diethyl α-naphthylchloromalonate as a sirup which was 86% pure (according to chlorine analysis) after short-path distillation at low pressure. Hydrogenation of the impure diethyl α-naphthylchloromalonate gave diethyl α-naphthylmalonate in 40% yield.

In a search for alternate routes for the synthesis of diethyl arylmalonates, ethyl arylcyanoacetates or arylmalononitriles, a number of reactions were investigated with negative results. These included the reaction of metal cyanides or liquid hydrogen cyanide with the benzoate and the benzenesulfonate of mandelonitrile, the reaction of diethyl bromomalonate with benzene in the presence of aluminum chloride, the reaction of diethyl tartronate with naphthalene in the presence of stannic chloride or hydrogen fluoride, and the reaction of mandelonitrile with liquid hydrogen cyanide.

EXPERIMENTAL[4]

Diethyl 9-phenanthryltartronate (I). Commercial (90%) phenanthrene was purified and brominated (18). The 9-bromophenanthrene was redistilled and recrystallized from 95% ethanol; m.p. 63.5–65°. Diethyl mesoxalate (12) was purified by conversion to its hydrate (diethyl dihydroxymalonate), which was washed with carbon disulfide (19), reconverted to diethyl mesoxalate by treatment with phosphorus pentoxide, extracted with ether and distilled from a small amount of phosphorus pentoxide (20); b.p. 98–100° (14 mm.).

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[3] Kindly supplied by Dr. Erich Mosettig, National Institutes of Health.

[4] Melting points are corrected and boiling points are uncorrected. We are indebted to Mr. S. M. Nagy and Mrs. Louise W. Spencer for analyses.

9-Phenanthrylmagnesium bromide was prepared by a procedure similar to one described by Bachmann (21) from 4.3 g. of magnesium turnings, 0.23 g. of iodine, 30 g. of 9-bromophenanthrene, and 70 ml. each of anhydrous ether and toluene. The mixture was stirred and heated under reflux for seven and one-half hours, at which time acidimetric titration indicated a 96–97% yield of the Grignard reagent. The suspension of 9-phenanthrylmagnesium bromide was diluted with 200 ml. of dry toluene, cooled to room temperature, and filtered to remove magnesium (through a stopcock sealed to the bottom of the flask in which the Grignard reagent was prepared). The Grignard reagent was added dropwise with vigorous stirring to a solution of 24.4 g. of purified diethyl mesoxalate in 300 ml. of dry toluene, cooled to −70° to −65° in a Dry Ice-bath, during one and three-quarters hours. The resulting orange suspension was stirred at −70° for forty-five minutes, warmed to 0°, and acidified by the dropwise addition of 18.5 ml. of 25% sulfuric acid at 0°, followed by 30 ml. of water (hydrolysis by saturated aqueous ammonium chloride solution in other preparations appeared to offer no advantage). The aqueous layer was extracted with ether and the combined organic layers were washed with 5% sodium bicarbonate solution and then with water until neutral. The solution was dried over magnesium sulfate and concentrated under reduced pressure. The residual red oil was dissolved in 250 ml. of dry cyclohexane containing 15% of ether and the product was allowed to crystallize at room temperature overnight and then at 5° until crystallization was complete. The product was separated by filtration and washed with 50 ml. of cold cyclohexane containing 15% of ether; yield 23.7 g. (58%) of a tan solid, m.p. 76.5–85°. No additional product crystallized from the mother liquors. The product was dissolved in 200 ml. of cyclohexane containing 15% of ether, heated with 2 g. of Darco, filtered, and cooled nearly to room temperature. The solution was decanted from a small amount of a dark oil which separated and allowed to stand first at room temperature and then at 5° until crystallization was complete. The yield of cream colored clusters of fine needles of diethyl 9-phenanthryltartronate (I), m.p. 87–87.5°, was 18.8 g. (46%). A sample from another preparation was obtained as a colorless solid with a constant melting point by crystallization from cyclohexane-ether, cyclohexane-benzene, and carbon tetrachloride; m.p. 88–88.5°. I gave a yellow solution in concentrated sulfuric acid which quickly darkened to an olive color.

Anal. Calc'd for $C_{21}H_{20}O_5$: C, 71.58; H, 5.72.

Found: C, 71.65; H, 5.90.

The use of diethyl mesoxalate as ordinarily prepared by the oxidation of diethyl malonate with nitrogen oxides and purified only by distillation in the preparation of I gave yields of 34–36%. An amount of phenanthrene equivalent to 16% of the original Grignard reagent was isolated from the mother liquors of one such preparaton. The phenanthrene was presumed to be formed by reaction of active hydrogen compounds in the diethyl mesoxalate with 9-phenanthrylmagnesium bromide, and purification of the ester by the procedure described resulted in an increase in the yield of I to 46%.

9-Phenanthrylglycolic acid (II). I was converted to II by a procedure similar to one used by Riebsomer and Irvine (12). A mixture of 1 g. of I and 0.8 g. of potassium hydroxide in 3 ml. of water containing a few drops of alcohol was heated on a steam-bath for six and one-half hours. After extraction with ether to remove any neutral material, 1.7 ml. of concentrated hydrochloric acid was added to the aqueous solution, which was heated on a steam-bath with stirring for an additional two hours. The product was extracted with ether, which was dried over magnesium sulfate and then concentrated. The residual oil was dissolved in dilute potassium hydroxide solution, which was extracted with ether and chloroform to remove any neutral material and then acidified with hydrochloric acid. The solid which separated was reprecipitated twice from alkaline solution by acidification, after treatment with Darco. The yield of 9-phenanthrylglycolic acid (II), m.p. 158–160° (dec.) was 0.49 g. (68%). Recrystallization from aqueous ethanol, ethyl acetate, and methanol gave colorless needles with a constant m.p. of 163–164° (dec.). II gave an olive color with concentrated sulfuric acid and a rather faint orange color with ferric chloride solution.

Anal. Calc'd for $C_{16}H_{12}O_3$: C, 76.18; H, 4.80.

Found: C, 75.86; H, 4.84.

Diethyl 9-phenanthrylchloromalonate (III). The method used for converting I to III was adapted from a procedure described for a similar transformation by Gerrard and French (22). A solution of 37 g. of I and 0.3 ml. of pyridine in 60 ml. of dry benzene was placed in a three-necked flask protected from the air with drying tubes and cooled to 5°. A solution of 13.8 g. of thionyl chloride in 50 ml. of dry benzene was added dropwise with stirring during ten minutes, with cooling to maintain a reaction temperature of 0–5°. After stirring for an additional thirty minutes the mixture was heated under reflux for one and one-half hours, at which time the initially vigorous evolution of gas had practically stopped. The solution was concentrated under reduced pressure and the residual oil was dissolved in benzene. After again concentrating and seeding, the oil which separated crystallized. The solid was triturated with 50 ml. of dry hexane containing 15% of ether, separated by filtration and washed with cold hexane containing 15% of ether. After drying briefly in a vacuum desiccator the solid was dissolved in 50 ml. of of hot carbon tetrachloride, filtered to remove pyridine hydrochloride, and cooled. The crystalline product was collected on a filter, washed with 10 ml. of cold carbon tetrachloride, and dried in a vacuum desiccator. III was obtained as fine pale yellow crystals, m.p. 91–110° (dec.); yield 32.9 g. (84%). A sample of III was recrystallized three times from dry carbon tetrachloride and three times from dry ethyl acetate; after five crystallizations the m.p. was 116–118.5° (dec.). Another crystallization from ethyl acetate lowered the m.p. to 97–100° (dec., immersed at 90° and heated at 1° per minute), but the material with m.p. 97–100° gave satisfactory analyses.

Anal. Calc'd for $C_{21}H_{19}ClO_4$: C, 68.01; H, 5.16; Cl, 9.56.

Found: C, 67.87; H, 5.22; Cl, 9.46.

Diethyl 9-phenanthrylmalonate (IV). A solution of 29 g. of III (m.p. 91–110°) in 230 ml. of purified, anhydrous dioxane was hydrogenated at room temperature and atmospheric pressure in the presence of 5 g. of palladium-on-Norit catalyst (23). The reduction required two hours and 1802 ml. (103%) of hydrogen was absorbed. The catalyst was separated by filtration, washed with dioxane, and the filtrate concentrated under reduced pressure to a volume of about 60 ml. The solution was poured into 300 ml. of water, which was then extracted with ether. The extract was washed with water, dried over magnesium sulfate and concentrated under reduced pressure to an oil which quickly solidified. After recrystallization from 50 ml. of 95% ethanol, 24.6 g. (94%) of IV was obtained as nearly colorless prisms, m.p. 106–108.5°. Concentration of the mother liquors yielded an additional 0.4 g. (2%), m.p. 83–96°. Recrystallization of the first crop from 200 ml. of cyclohexane gave 23.5 g. (89%) of IV as colorless crystals, m.p. 108–109°. An analytical sample crystallized to constant melting point from 95% ethanol, cyclohexane, and hexane had m.p. 110–110.5°.

Anal. Calc'd for $C_{21}H_{20}O_4$: C, 74.98; H, 5.99.

Found: C, 74.78; H, 5.85.

IV was converted to *9-phenanthrylacetic acid* (V) for identification, by a procedure similar to the one used for converting I to II. IV (0.801 g.) was heated on a steam-bath with 1.06 g. of potassium hydroxide in 4 ml. of water for five hours. After extraction with ether, the aqueous solution was acidified with an excess of hydrochloric acid and heated for an additional two hours. Extraction with ether and recrystallization of the acid from absolute ethanol gave 0.387 g. (69%) of V, m.p. 221.5–224°. Reprecipitation of the acid from alkaline solution by acidification and two recrystallizations from methanol raised the m.p. of V to 224–225°. V did not depress the m.p. of an authentic sample (17).

Diethyl α-naphthylmalonate. α-Naphthylmagnesium bromide was prepared from 5.3 g. of magnesium, 45 g. of redistilled α-bromonaphthalene, and 110 ml. of dry ether by the procedure of Gilman, St. John, and Schulze (24), except that the Grignard reagent was dissolved by addition of 135 ml. of dry toluene (rather than benzene). The Grignard reagent was added dropwise with stirring during one and one-quarter hours to a solution of 38 g. of diethyl mesoxalate (purified only by redistillation) in 100 ml. of dry toluene at a reaction temperature of −70 to −60°. The resulting suspension was stirred for one-half hour at −70° and then acidified with dilute sulfuric acid at about −10°. The organic layer and a benzene extract of the aqueous layer were combined, washed with water, dried over magnesium sulfate and treated with Darco. After filtration and concentration 58 g. of a viscous

red sirup was obtained which failed to crystallize. After a short-path distillation at a bath temperature of 130–165° and 0.01 mm. the product remained a sirup.

Diethyl O-benzoyl-α-naphthyltartronate was prepared as a crystalline derivative of the impure diethyl α-naphthyltartronate by a procedure based on one used in a similar case by Jackson and Phinney (25). The sirup (3 g.) was heated with 15 ml. of benzoyl chloride at 110° for seven hours, after which the excess benzoyl chloride was removed under reduced pressure. The residue was dissolved in toluene, which was removed under reduced pressure. After repetition of this process a benzene solution of the residue was treated with Darco, again concentrated, and the red glassy residue was heated at 110° and 0.1 mm. for several hours. On standing, partial crystallization occurred, and the crystalline solid was separated by trituration with 15 ml. of cold absolute ethanol and filtration; yield 0.8 g. (20%), m.p. 109.5–110.5°. Recrystallization from aqueous ethanol and from methylcyclohexane gave diethyl O-benzoyl-α-naphthyltartronate with a constant m.p. of 111–111.5°.

Anal. Calc'd for $C_{24}H_{22}O_6$ C, 70.92; H, 5.46.

Found: C, 70.89; H, 5.63.

Preparation of the benzoate by reaction of diethyl α-naphthyltartronate with benzoyl chloride in pyridine or by treating the bromomagnesium compound formed by addition of α-naphthylmagnesium bromide to diethyl mesoxalate with benzoyl chloride failed to give a higher yield.

The crude diethyl α-naphthyltartronate was converted to diethyl α-naphthylchloromalonate by reaction with thionyl chloride in the presence of a small amount of pyridine in the same manner that I was converted to III. The *diethyl α-naphthylchloromalonate* was obtained as a sirup which after two short-path distillations at a bath temperature of 110–125° and 0.02–0.04 mm. was 86% pure (Calc'd Cl, 11.05; Found, 9.46); n_D^{25} 1.5550; yield 52%. Hydrogenation of 2.09 g. of this crude product in a manner similar to that used for preparation of IV from III gave 0.75 g. (40%) of *diethyl α-naphthylmalonate* after crystallization from hexane; m.p. 57–60.5°. Recrystallization from cyclohexane and from a hexane-pentane-ether mixture raised the m.p. to 62–63°, in agreement with the reported value of 62° (26).

Anal. Calc'd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34.

Found: C, 71.18; H, 6.42.

Diethyl α-naphthylmalonate was prepared by this route as a model case, and undoubtedly is better prepared from ethyl α-naphthylacetate (26).

SUMMARY

Diethyl 9-phenanthrylmalonate has been prepared by the addition of 9-phenanthrylmagnesium bromide to diethyl mesoxalate at −70°, conversion of the resulting diethyl 9-phenanthryltartronate to diethyl 9-phenanthrylchloromalonate by reaction with thionyl chloride, and removal of the chlorine by catalytic hydrogenation.

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PYRROLIDYL ALKANOLS

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In connection with other work in this laboratory a variety of pyrrolidine substituted alcohols were needed. In recent communications from this laboratory the preparation of 3-(1-pyrrolidyl)propanol (1), 1-(1-pyrrolidyl)propanol-2 (2), 2-(2,5-dimethyl-1-pyrrolidyl)ethanol (2), 1-(2,5-dimethyl-1-pyrrolidyl)propanol-2 (2), 2-(2,4-dimethyl-1-pyrrolidyl)ethanol (2), and 1-(2,4-dimethyl-1-pyrrolidyl)propanol-2 (2) was reported. A search of the literature revealed that only the 2-(1-pyrrolidyl)ethanol (3) and 2-(2-ethyl-1-pyrrolidyl)ethanol (4) had previously been prepared.[1] In this communication a number of other pyrrolidyl alkanols are reported and their methods of preparation described.

Since no single method of preparation was suitable for all the compounds desired a variety of procedures was used. Some of these were modifications of well known methods for the preparation of tertiary amino alcohols, as, for example, the alkylation of pyrrolidine with the appropriate chlorohydrin (method I). A number of amino alcohols have previously been prepared by the reduction of amino esters, aldehydes, or ketones. For these reductions sodium and alcohol, catalytic hydrogenation, or aluminum isopropoxide have been used with varying degrees of success. It has now been found that lithium aluminum hydride (6) is very satisfactory for these reductions (method H). This reagent has also been found to be suitable for the reduction of N-alkanol substituted pyrrolidones[2] or N-alkanol substituted succinimides to the corresponding N-alkanolpyrrolidines. Heretofore similar reductions using active metals, catalytic, or electrolytic methods have given low yields.

Several attempts were made to prepare 2-(1-pyrrolidyl)-2-methylpropanol from α-(1-pyrrolidyl)isobutyronitrile, which is easily obtained from acetone cyanohydrin and pyrrolidine. It was planned to convert the nitrile to the corresponding ester and reduce this with lithium aluminum hydride; however the ester was obtained only in very small yield. This pyrrolidyl alcohol was finally prepared in good yield by closing the pyrrolidine ring on 2-amino-2-methylpropanol with tetramethylene dibromide (method J).

Table I lists the properties of a variety of intermediate compounds and Table II lists the pyrrolidyl alkanols. Each method of preparation is illustrated by one example in the experimental part. It will be noted that many of these compounds can exist in more than one stereoisomeric form; however no attempt was made to separate any of them, and it is therefore probable that some of the products

[1] Blicke and Blake (5) prepared the benzoate of 1-(1-pyrrolidyl)-2-methylbutanol-2 but did not characterize the intermediate pyrrolidyl alcohol.

[2] Since the completion of this work the report of Karrer and Portmann (7) has appeared in which 2-carbethoxypyrrolidone-5 was reduced with lithium aluminum hydride to 2-hydroxymethylpyrrolidine.

TABLE I
INTERMEDIATE COMPOUNDS

No.	STRUCTURAL FORMULA	PREP. METHOD	YIELD %	B.P., °C.	MM	n^{25}_{D}	d^{25}_{4}	EMPIRICAL FORMULA	% NITROGEN[a] Calc'd	% NITROGEN[a] Found
1	$CH_2CH_2CH_2CH_2NCH(CH_3)COOC_2H_5$	A	91.5	84	12	1.4450	0.9724	$C_9H_{17}NO_2$	8.18	8.21
2	$CH_2CH_2CH_2CH_2NCH_2CH(CH_3)COOCH_3$	B	79.5	86	13	1.4462	.9713	$C_9H_{17}NO_2$	8.18	8.12
3	$CH_2CH_2CH_2CH_2NCH(CH_3)CH_2COOC_4H_9$	B[b]	77	71	0.05	1.4548	—	$C_{12}H_{23}NO_2$	6.59	6.53
4	$CH_2CH_2CH_2CH_2NCH(CH_3)COCH_3$	A[c]	81	73	14	1.4522	.9331	$C_8H_{15}NO$	9.92	9.80
5	$CH_2CH_2CH_2CH_2NC(CH_3)_2CN$	C	88.7	75	12	1.4511	.9267	$C_8H_{14}N_2$	20.28	20.10
6	$CH_2CH_2CH_2CH_2NC(CH_3)_2COOCH_3$	D	4.0	90	20	1.4518	—	$C_9H_{17}NO_2$	8.18	8.21
7	$CH_2CH_2CH_2CH_2NCH_2C(CH_3)_2CHO$	E	42.3	97	32	1.4565	—	$C_9H_{17}NO_2$	9.02	8.95
8	$CH(CH_3)CH_2CH_2C(O)NCH_2CH_2OH$[d]	F	95	167	12	1.4883[e]	1.1002	$C_7H_{13}NO_2$	9.78	9.36
9	$CH(CH_3)CH_2CH_2C(O)NCH_2CH_2CH_2OH$	F[f]	95.6	180	14	1.4855	—	$C_8H_{15}NO_2$	8.91	8.81
10	$CH(CH_3)CH_2C(CH_3)_2C(O)NCH_2CH_2OH$	F[g]	96.3	157	13	1.4727	1.0239	$C_9H_{17}NO_2$	8.18	8.16
11	$CH(CH_3)CH(CH_3)CH_2C(O)NCH_2CH_2OH$	F[h]	94.4	174	14	1.4850	—	$C_8H_{15}NO_2$	8.91	9.17
12	$C(O)CH_2CH(CH_3)C(O)NCH_2CH_2OH$	G	86.4	102	0.01	1.4970	—	$C_7H_{11}NO_3$	8.91	9.17
13	$C(O)CH(CH_3)CH(CH_3)C(O)NCH_2CH_2OH$	G[i]	92.2	167	12	1.4878	—	$C_8H_{13}NO_3$	8.18	8.54
14	$C(O)C(CH_3)_2CH_2C(O)NCH_2CH_2OH$	G[j]	87.6	167	14	1.4870	—	$C_8H_{13}NO_3$	8.18	8.38

[a] Nitrogen analyses by Mr. Harold Emerson and staff of our microanalytical laboratory. [b] Butyl crotonate was used in place of methyl methacrylate. The product distilled over considerable range (120–140° at 17 mm.), probably due to some dissociation during the distillation; yield 77% n^{25}_{D} 1.4535. This crude material was used for the reduction with lithium aluminum hydride. A small sample was redistilled under high vacuum through a short column giving a pure product, with the properties listed above. [c] 3-Bromobutanone-2 [Catch, Elliott, Hey, and Jones, *J. Chem. Soc.*, 272 (1948)] was used in place of ethyl α-bromopropionate and the reaction mixture was only refluxed for fifteen minutes after the addition and then allowed to stand over night. [d] Bachman and Mayheu, *J. Org. Chem.*, **10**, 243 (1945), report the preparation of this pyrrolidone by the alkylation of 5-methylpyrrolidone-2 with ethylene chlorohydrin giving b.p. 144–147° (7 mm.), n^{20}_{D} 1.4480, d^{20}_{4} 1.006. [e] n^{20}_{D} 1.4900. [f] Propanol amine [Schnider, *Jubilee Vol. Emil Barell*, 85–91 (1946)] was used in place of ethanol amine. [g] Mesitonic acid [Lapworth, *J. Chem. Soc.*, **85**, 1220 (1904)] was used in place of levulinic acid. [h] β-Methyllevulinic acid [Pauley, Gilmore, and Will, *Ann.*, **403**, 119 (1914)] was used in place of levulinic acid. [i] α,α'-Dimethylsuccinic anhydride was used in place of methylsuccinic acid. [j] α,α-Dimethyl succinic acid [Vogel, *J. Chem. Soc.*, 2020 (1928)] was used in place of methylsuccinic acid.

TABLE II

Pyrrolidyl Alkanols

Formula	k	Prep. Method	Yield %	B.p., °C.	Mm.	n_D^{25}	d_4^{25}	Formula	Neut. Equiv.		% Nitrogen[a]	
									Calc'd	Found	Calc'd	Found
$CH_2CH_2CH_2CH_2NCH(CH_3)CH_2OH$	1	H	79.0	80	11	1.4758	0.9733	$C_7H_{15}NO$	129.20	128.8	10.84	10.96
$CH_2CH_2CH_2CH_2NCH_2CH_2CH_2CH_2OH$	—	I	72.1	113	12	1.4705	.9463	$C_8H_{17}NO$	143.23	144.3	9.78	9.71
$CH_2CH_2CH_2CH_2NCH_2CH_2CH(CH_3)OH$	—	H[b]	51.7	87	13	1.4611	.9350	$C_8H_{17}NO$	143.23	150.8	9.78	9.34
$CH_2CH_2CH_2CH_2NCH(CH_3)CH_2CH_2OH$	3	H	74.6[c]	114	21	1.4742	.9596	$C_8H_{17}NO$	143.23	146.1	9.78	9.66
$CH_2CH_2CH_2CH_2NCH_2CH(CH_3)CH_2OH$	2	H[d]	89.7	91	12	1.4620	.9332	$C_8H_{17}NO$	143.23	146.3	9.78	9.61
$CH_2CH_2CH_2CH_2NCH(CH_3)CH(CH_3)OH$	4	H	92.6	79	13	1.4610	.9367	$C_8H_{17}NO$	143.23	147.2	9.78	9.67
$CH_2CH_2CH_2CH_2NC(CH_3)_2CH_2OH$	—	J	75.5	87	12[e]	1.4720[f]	.9624[f]	$C_8H_{17}NO$	143.23	143.3	9.78	9.80
$CH_2CH_2CH_2CH_2NCH_2C(CH_3)_2CH_2OH$	7	K	41.7	111	26	1.4609	.9248	$C_9H_{19}NO$	157.25	166.0	8.91	8.61
$CH_2CH_2CH_2CH_2N(CH_2)_3CH(CH_3)OH$	—	L[g]	85	111	12	1.4652	.930	$C_9H_{19}NO$	157.25	160.2	8.91	9.06
$CH_2CH_2CH_2CH_2NCH_2CH_2OCH_2CH_2OH$	—	[h]	—	122	13	1.4691	1.0064	$C_8H_{17}NO_2$	159.23	161.4	8.80	8.73
$CH_2CH_2CH_2CH(CH_3)NCH_2CH_2OH$	8	H[i]	76.0	81	16	1.4680	0.9537	$C_7H_{15}NO$	129.20	130.9	10.84	10.51
$CH_2CH_2CH_2CH(CH_3)NCH_2CH_2CH_2OH$	9	H[i]	91.0	100	18	1.4672	.9384	$C_8H_{17}NO$	143.23	144.0	9.78	9.64, 9.86
$CH_2CH_2CH(CH_3)CH_2NCH_2CH_2OH$	12	H[j]	68.1[c]	105	45	1.4640	.9466	$C_7H_{15}NO$	129.20	132.5	10.84	10.20
$CH_2CH_2CH(CH_3)CH(CH_3)NCH_2CH_2OH$	11	H[i]	89.4	86	13	1.4661	.9411	$C_8H_{17}NO$	143.23	144.0	9.78	9.60, 9.96
$CH_2CH_2C(CH_3)_2CH_2NCH_2CH_2OH$	14	H[j]	—	81	13	1.4580	.9209	$C_8H_{17}NO$	143.23	147.0	9.78	9.68
$CH_2CH(CH_3)CH(CH_3)CH_2NCH_2CH_2OH$	13	H[j]	61.6	86	12	1.4594	.9248	$C_8H_{17}NO$	143.23	146.3	9.78	9.15
$CH_2C(CH_3)_2CH_2CH(CH_3)NCH_2CH_2OH$	10	H[i]	88.2	84	14	1.4535	.9042	$C_9H_{19}NO$	157.25	159.8	8.91	8.74, 9.09

[a] Footnote [a] Table I. [b] Equimolar quantities of methyl vinyl ketone and pyrrolidine were mixed and reduced with lithium aluminum hydride without isolating the intermediate methyl β-(1-pyrrolidyl)ethyl ketone. The yield is the over-all yield. [c] This yield is based on the crude intermediate which was used for the lithium aluminum hydride reduction. [d] This same compound was also prepared in 17.4% yield, by the addition of pyrrolidine (1 mole) to methallyl alcohol (3.55 moles) in which 1 mole of sodium had been dissolved. [e] This amino alcohol is a solid, freezing point 30°. [f] Taken at 30° on the liquid. [g] This compound was prepared by Dr. Robert H. Reitsema in this Laboratory. [h] This compound was isolated by Dr. Wm. Bradley Reid, Jr. in this Laboratory as a by-product, in about 10% yield, during the preparation of 2-(1-pyrrolidyl)ethanol from pyrrolidine and ethylene oxide. [i] Prepared by the reduction of the corresponding N-alkanolpyrrolidone. [j] Prepared by the reduction of the corresponding N-alkanol succinimide. [k] Number refers to compound in Table I used as starting material.

described represent mixtures of diastereoisomers and *cis-trans* forms as well as racemic mixtures.

EXPERIMENTAL

Method A. Ethyl α-(1-pyrrolidyl)propionate. To a solution of 181 g. (1 mole) of ethyl α-bromopropionate in 200 ml. of benzene was slowly added 148 g. (2.1 moles) of pyrrolidine with stirring. The reaction was exothermic and the solvent refluxed. After the addition was complete the mixture was heated under reflux for one hour, cooled, poured into ice-water, and acidified with dilute hydrochloric acid. The aqueous solution was separated, washed with ether, and made basic with cold sodium hydroxide. The basic ester was extracted with four 200-ml. portions of ether, washed with water, and dried over potassium carbonate. After removal of the solvent the product was distilled through a short column, giving 156.7 g. of a colorless liquid with the properties listed in Table I.

Method B. Methyl β-(1-pyrrolidyl)isobutyrate. A mixture of 100 g. (1 mole) of methyl methacrylate (stabilized with 0.006% hydroquinone) and 71 g. (1 mole) of pyrrolidine was refluxed for three hours and then distilled *in vacuo*. After removing a small forerun the product was collected giving 136.4 g. of a colorless liquid with the properties listed in Table I.

Method C. α-(1-Pyrrolidyl)isobutyronitrile. To 170 g. (2 moles) of acetone cyanohydrin was slowly added 142 g. (2 moles) of pyrrolidine. The mixture was cooled slightly to keep the temperature below the boiling point. The water which separated was saturated with sodium sulfate by shaking. The aqueous layer was removed, and the organic solution was dried over calcium sulfate and distilled through a short column, giving 245 g. of colorless liquid with the properties listed in Table I.

Method D. Methyl α-(1-pyrrolidyl)isobutyrate. To 69.1 g. (0.5 mole) of crude (undistilled) α-(1-pyrrolidyl)isobutyronitrile was added 400 ml. of concentrated hydrochloric acid, and the mixture was heated on a steam-bath for twenty hours. The solution was distilled to dryness, the residue was boiled with absolute methanol and filtered from ammonium chloride. The solvent was removed *in vacuo* and the residue was again taken up in 500 ml. of absolute methanol and saturated with hydrogen chloride gas with cooling. After standing at about 25° for four days the mixture was distilled to dryness *in vacuo*. The residue was diluted with water, made basic with sodium hydroxide solution, and continuously extracted with ether for six hours. The ether solution was dried over potassium carbonate and distilled, giving only 3.4 g. of colorless liquid with the properties listed in Table I.

Method E. 2,2-Dimethyl-3-(1-pyrrolidyl)propionaldehyde. A mixture of 71.1 g. (1 mole) of pyrrolidine, 81 ml. (1 mole) of concentrated hydrochloric acid, and 81 ml. (1 mole) of 37% aqueous formaldehyde was heated to the boiling point and then 79.3 g. (1.1 moles) of isobutyraldehyde was slowly added with stirring during three-fourths hour. The refluxing was continued for one hour and then 50 ml. more formaldehyde solution was added. After refluxing for one and one-fourth hours more and standing three days the mixture was made basic with cold 40% sodium hydroxide and extracted five times with ether. The ether solution was dried over potassium carbonate and distilled through a short column giving 65.7 g. of nearly colorless liquid with the properties listed in Table I.

Method F. 1-(2-Hydroxyethyl)-5-methylpyrrolidone-2. A suspension of 0.2 g. of platinum oxide catalyst in 25 ml. of absolute ethanol was hydrogenated to platinum and then a solution of 34.8 g. (0.3 mole) of levulinic acid and 37.8 g. (0.62 mole) of ethanolamine in 75 ml. of absolute alcohol was added and the mixture was hydrogenated at about 50 lbs. pressure and room temperature. Approximately the theoretical quantity of hydrogen was absorbed in less than four hours. After distilling off the alcohol and the excess ethanolamine the pyr rolidone was distilled twice through a short column giving a liquid with the properties listed in Table I.

Method G. N-(2-Hydroxyethyl)-α-methylsuccinimide. A mixture of 66 g. (0.5 mole) of

methylsuccinic acid[3] and 73.4 g. (1.2 moles) of ethanolamine in a Claisen flask was placed in an oil-bath, the temperature of which was gradually raised to 260° and kept at about this temperature until the distillation practically ceased (about one-half hour). The residue was distilled *in vacuo*, giving a viscous oil which was redistilled through a short column giving 67.8 g. of light yellow liquid which contained a small amount of solid impurity. The physical properties are listed in Table I.

Method H. 2-(1-Pyrrolidyl)propanol. A 1-l. three-necked flask was fitted with a reflux condenser, stirrer, and dropping-funnel. In it was placed 21.3 g. (0.56 mole) of lithium aluminum hydride (6),[4] and 250 ml. of absolute ether. The mixture was refluxed until most of the hydride was dissolved and then a solution of 157.3 g. (0.92 mole) of ethyl α-(1-pyrrolidyl)propionate in 100 ml. of dry ether was slowly added with vigorous stirring at such a rate that the ether refluxed smoothly. When the addition was complete the mixture was refluxed for one-half hour longer and then decomposed by very cautiously adding dropwise, with vigorous stirring, 50 ml. of water. Sufficient dilute hydrochloric acid was cautiously added to dissolve the precipitated aluminum hydroxide and the aqueous layer was separated and washed with ether. A large excess of strong sodium hydroxide solution was added to the acid solution giving a milky suspension which was continuously extracted with ether for six hours. After drying over potassium carbonate the ether was removed and the product distilled through a short column giving a colorless liquid with the properties listed in Table II.

Method I. 4-(1-Pyrrolidyl)butanol. A 1-l. three-necked flask was fitted with a stirrer and two efficient condensers. In the flask was placed 142.2 g. (2 moles) of pyrrolidine and then 108.6 g. (1 mole) of tetramethylene chlorohydrin was added all at once with stirring. The exothermic reaction caused vigorous reflux for a few minutes, and then the mixture was heated on a steam-bath for one hour. After cooling 140 ml. of 40% sodium hydroxide solution was added. The amine layer was separated and saturated with potassium carbonate. The aqueous layers and precipitated salts were extracted with ether which was added to the amine layer and dried with potassium carbonate. After removal of the ether and excess pyrrolidine the product was distilled through a short column giving a colorless liquid with the properties listed in Table II.

Method J. 2-(1-Pyrrolidyl)-2-methylpropanol. In a flask fitted with a reflux condenser and an efficient stirrer was placed 44.6 g. (0.5 mole) of 2-amino-2-methylpropanol,[5] 108 g. (0.5 mole) of tetramethylene dibromide, and 200 ml. of toluene. After refluxing for three hours with stirring, 84 g. (1 mole) of sodium bicarbonate was added and the mixture was refluxed with vigorous stirring for an additional fifteen hours. After cooling 80 ml. of 50% sodium hydroxide solution was added. The organic layer was separated, enough water was added to the aqueous layer to dissolve the salt, and the solution was continuously extracted with ether for nine hours. The ether extract was added to the toluene solution, dried over potassium carbonate and distilled. The product solidified in the receiver, f.p. 27.5°. This was treated in acid solution with nitrous acid to remove any primary amine. The solution was extracted with ether, made basic, again extracted with ether, dried and redistilled. The freezing point was raised only 2.5°. The properties are listed in Table II.

Method K. 3-(1-Pyrrolidyl-2,2-dimethylpropanol. A mixture of 61.5 g. (0.396 mole) of 3-(1-pyrrolidyl),2,2-dimethylpropionaldehyde, 350 ml. of isopropanol, and 40.8 g. (0.2 mole) of aluminum isopropoxide was slowly distilled through an efficient column for six hours. By this time the test for acetone in the distillate was nearly negative and the mixture had become very dark. After cooling, 200 ml. of 10% sodium hydroxide solution was added. The upper layer was removed and saturated with potassium carbonate. The two aqueous layers

[3] The methylsuccinic acid was prepared by a procedure similar to that described by Brown (8) except that methyl methacrylate was used in place of ethyl crotonate. The yield was 47%.

[4] Obtained from Metal Hydrides Incorporated, Beverly, Mass.

[5] From Commercial Solvents Corp., Terre Haute, Ind.

were combined and extracted six times with ether. The ether solution was combined with the isopropanol solution and dried over potassium carbonate. After removal of the solvent the product was distilled twice through a short column giving a colorless liquid with the properties listed in Table II.

Method L. 5-(1-Pyrrolidyl)pentanol-2. A solution of 65.5 g. (0.422 mole) of 5-pyrrolidylpentanone-2 (9) in 60 ml. of methanol was hydrogenated in the presence of 5 g. of Raney nickel catalyst at 1100 lbs. pressure and 100° for three hours. Approximately the theoretical quantity of hydrogen was absorbed and after filtration from catalyst and distillation a yield of 57.2 g. (85%) of the amino alcohol was obtained. A sample was redistilled giving a colorless liquid with the properties listed in Table II.

SUMMARY

1. Seventeen new pyrrolidyl alkanols have been prepared. Many different straight- and branched-chain alkanol groups have been attached to the nitrogen of pyrrolidine rings, some of which have been substituted with methyl groups in various positions.

2. Lithium aluminum hydride has been found to be very satisfactory for the reduction of pyrrolidyl substituted esters or ketones to pyrrolidyl alcohols, and for the reduction of substituted pyrrolidones and succinimides to pyrrolidines.

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[Contribution from the Research Laboratory of Endo Products, Inc. and the Department of Chemistry, Brooklyn College]

N-2-PYRIDYLALKANOLAMINES AND ESTERS

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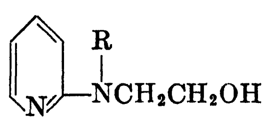
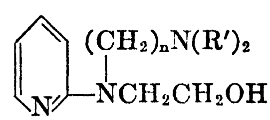
Despite the occurrence of natural compounds with pharmacological activity containing the pyridine nucleus, few attempts at the introduction of this group into the structures of synthetic drugs appear to have been reported. While the work, herein reported, was in progress, reports on the synthesis of 2-pyridyl substituted ethylene diamines as histamine antagonists (1), and longer chained 2-pyridylalkylenediamines as potential antimalarials (2) have appeared. In addition the antihistaminic activity of N,N-dimethyl-N[1]-(*p*-methoxybenzyl)-N[1]-(2-pyridyl)ethylenediamine has been described (3).

This work was directed to the preparation of alkanolamines containing the pyridine nucleus, so as to examine the influence of this group in various types of pharmacological agents in which the alkanolamine group is an essential contributor to the pharmacological activity, *e.g.*, esters of benzoic acid, *p*-aminobenzoic acid (local anesthetic) and diphenylacetic acid (spasmolytic). Syntheses of N-2-pyridylamino alcohols of types (I) and (II) were undertaken. In addition 2-methyl-2-(2-pyridyl)amino-1,3-propanediol (III) was prepared.



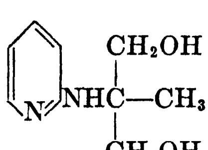
(I)

Ia $R = H$
Ib $R = C_2H_5$
Ic $R = n\text{-}C_4H_9$
Id $R = C_6H_5CH_2$
Ie $R = HOCH_2CH_2$



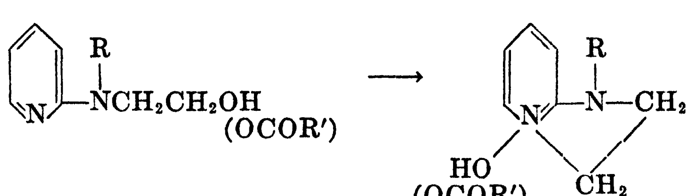
(II)

IIa $n = 2, R' = C_2H_5$
IIb $n = 2, R' = n\text{-}C_4H_9$
IIc $n = 3, R' = C_2H_5$
IId $n = 3, R' = n\text{-}C_4H_9$



(III)

Equation 1



Of the various methods available for the synthesis of compounds of these types (1, 2, 4, 5) a modification of that by which Bremer (4) prepared Ia was selected as affording the most conveniently applicable general procedure. The higher-boiling and more reactive 2-bromopyridine was used in preference to 2-chloropyridine (4), thus avoiding the need for carrying out the reaction in sealed tubes.

The amino alcohols required for the preparation of type (I) compounds and compound (III) were readily available from commercial sources or by described synthesis. The dialkylaminoalkyl ethanolamines for the preparation of type II were hitherto unknown, but were made by the interaction of the appropriate dialkylaminoalkyl chloride and excess ethanolamine in boiling dioxane. The properties and yields of these intermediates are listed in Table I. The properties

TABLE I

DIALKYLAMINOALKYLAMINOETHANOLS

$(R')_2N(CH_2)_nNHCH_2CH_2OH$

PRODUCT		REAGENTS					B.P., °C/MM.	YIELD		ANALYSIS N, %	
R'	n	$(R')_2N(CH_2)_nCl$		$NH_2CH_2CH_2OH$		Dioxane, cc.		Gms.	%	Calc'd	Found
		Gms.	Moles	Gms.	Moles						
C_2H_5	2	136.6	1.01	183	3.03	430	140–143/24	78	48	17.48	17.33
C_2H_5	3	67	0.45	82.5	1.35	260	146–147/14[a]	48.5	66	16.08	16.23
n-C_4H_9	2	256	1.34	244	4.01	700	136–137/2.5	188.5	65	16.30	16.01
n-C_4H_9	3	258	1.25	380	6.22	400	143–147/2	244	85	12.16	12.10

[a] Hydrochloride, recrystallized from n-propanol, m.p. 181–182.5°. *Anal.* N, Calc'd 11.33%; Found 11.45%.

and yields of the new pyridine derivatives (I b–e, II a–d, and III) are given in Table II.

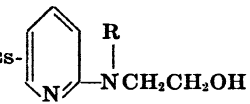
The preparation of esters of these alcohols was not unattended with difficulties inherent in the structures of these compounds. It appeared from the experience of Bremer (4, 6) that any but the mildest conditions for esterification would result in cyclization of the alcohols or their esters to the isomeric dihydroimidazo[1,2-a]-pyridine base or salt (Equation 1).

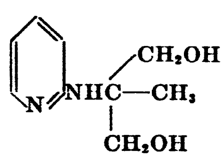
This likelihood is possibly somewhat minimized where R is not H, due to the impossibility of the existence of the tautomeric ketimine of 2-amino pyridine postulated (6) as an intermediate in such cyclizations. In order to avoid completely this complication, the alcohols were esterified at the lowest possible temperature at which reaction occurred with the acyl chlorides.

In many cases it was not possible to prepare crystalline salts of the esters. Purification by distillation was not attempted because of the instability of the compounds at elevated temperature. The crude compounds were simply dried in a high vacuum at room temperature and the resulting oils submitted for pharmacological testing.

The pyridyl ethanolamines were tested for antimalarial activity by the Survey

TABLE II

2-PYRIDYLETHANOLAMINES- 

No.	R	REAGENTS: α-Bromopyridine Gms.	REAGENTS: α-Bromopyridine Moles	REAGENTS: $RNHCH_2CH_2OH$ Gms.	REAGENTS: $RNHCH_2CH_2OH$ Moles	REAGENTS: Cumene, cc.	REACTION CONDITIONS: Time, hrs.	REACTION CONDITIONS: Bath Temp., °C.	B.P., °C/MM.	YIELD Gms.	YIELD %	FORMULA (SN NO.)	ANALYSIS, % N Calc'd	ANALYSIS, % N Found
Ia	H[a]	158	1.0	244	4.0	None	24	160	166–168/9	114.3	83	$C_7H_{10}N_2O$ (SN 2802)	20.13	19.86
Ib	C_2H_5	79	0.5	89	1.0	None	12	145	157–158/15	53.1	64	$C_9H_{14}N_2O$ (SN 2803)	16.86	16.88
Ic	n-C_4H_9	79	0.5	117	1.0	None	50	154	125–127/1	62.6	64.5	$C_{11}H_{18}N_2O$ (SN 2804)	14.42	14.49
Id	$C_6H_5CH_2$[b]	79	0.5	151	1.0	None	21	166	154–159/1	68.9	60	$C_{14}H_{16}N_2O$	[c]	[c]
Ie	$HOCH_2CH_2$	158	1.0	182	2.0	None	389	100	163/1	48.2	26.5	$C_9H_{14}N_2O_2$	15.37	15.42
IIa	$(C_2H_5)_2NCH_2CH_2$	29.7	0.19	72.5	0.47	87	14.5	170	154–158/2	20.5	46	$C_{13}H_{23}N_3O$ (SN 4229)	17.71	17.69
IIb	$(C_4H_9)_2NCH_2CH_2$	67.5	0.43	237	1.07	300	14.5	170	190–192/2	49	39	$C_{17}H_{31}N_3O$ (SN 4230)	14.32	14.27
IIc	$(C_2H_5)_2N(CH_2)_3$	16.7	0.105	43	0.26	55	16	170	160–162/1	15.5	58.5	$C_{14}H_{25}N_3O$ (SN 4227)	16.72	16.73
IId	$(C_4H_9)_2N(CH_2)_3$	31.8	0.2	116.5	0.5	163	18	170	194–200/2	31	50	$C_{19}H_{33}N_3O$ (SN 4228)	13.67	13.55
III		158	1.0	420	4.0	None	89	161–168	189–191/11	36.4	20	$C_9H_{14}N_2O_2$	15.37	15.41

[a] Bremer, *Ann.*, **521**, 286 (1936); obtained by us as a solid, m.p. 65–68° with previous softening at 57.5°.
[b] Rumpf and Kwass, *Bull. soc. chim.*, **10**, 347 (1943).
[c] Purified for analysis as the picrate, m.p. 132.5–134°; *Anal.* Calc'd for $C_{20}H_{19}N_5O_8$: N, 15.31; Found: N, 15.26.

of Antimalarial Drugs under the SN numbers given in Table II. No important activity was disclosed.

EXPERIMENTAL

Preparation of dialkylaminoalkylaminoethanols (Table I). The appropriate, freshly distilled, free dialkylaminoalkyl chloride was dissolved with ethanolamine in dioxane in the quantities indicated in Table I. The mixture was boiled under reflux overnight (14–16 hours). The product usually separated in the course of the reaction as an oil. The dioxane was

TABLE III

ESTERS OF 2-PYRIDYLAMINOALCOHOLS

ALCOHOL	ESTER[g]	M.P., °C	ESTER FORMULA	ANALYSIS % N		PICRATE		ANALYSIS, % N	
				Calc'd	Found	M.P., °C	Formula	Calc'd	Found
Ia	A					171–173.5[a]	$C_{20}H_{17}N_5O_9$	14.86	14.78
Ia	B	73–74[b]	$C_{21}H_{20}N_2O_2$	8.43	8.82	131 (sinters)	$C_{27}H_{23}N_5O_9$	12.47	12.34
Ia	C	162.5–165[c]	$C_{14}H_{16}ClN_3O_2$	14.31	14.71				
Ib	A		$C_{16}H_{18}N_2O_2$	10.36	10.30	146–147[d]	$C_{22}H_{21}N_5O_9$	14.03	14.04
Ib	B	83–84[b]	$C_{23}H_{24}N_2O_2$	7.77	7.69				
Ib	C	93–93.5[b]	$C_{16}H_{19}N_3O_2$	14.73	14.73				
Ic	A		$C_{18}H_{22}N_2O_2$	9.39	8.91	120–121[e]	$C_{24}H_{25}N_5O_9$	13.28	13.24
Ic	C	76–76.5[b]	$C_{18}H_{23}N_3O_2$	13.41	13.39				
Id	A		$C_{21}H_{20}N_2O_2$	8.43	8.09	133–135[a]	$C_{27}H_{23}N_5O$	12.47	12.26
Id	B	93–94[b]	$C_{28}H_{26}N_2O_2$	6.63	6.59				
Id	C	103–103.5[a]	$C_{21}H_{21}N_3O_2$	12.10	12.09				
Ie	A[f]		$C_{23}H_{22}N_2O_4$	7.18	6.82	134–135[a]	$C_{29}H_{25}N_5O$ 1	11.31	11.14
Ie	B		$C_{37}H_{34}N_2O_4$	4.91	4.55	116.5–117.5	$C_{43}H_{37}N_5O_{11}$	8.76	8.87
IIc	A					136–137[e] softens at 128	$C_{33}H_{35}N_9O_{16}$	15.31	15.46

[a] Recrystallized from ethanol.
[b] Recrystallized from methanol.
[c] Hydrochloride, recrystallized from acetone–ethanol.
[d] Recrystallized from acetone.
[e] Recrystallized from *n*-propanol.
[f] Dibenzoate.
[g] A is benzoate; B is diphenylacetate; C is *p*-aminobenzoate.

removed *in vacuo*. The residue was shaken with a saturated solution of potassium carbonate equal to 1.1 equivalents of the alkyl chloride. The mixture was extracted with ether, and the ether extracts, after being dried over potassium carbonate, were concentrated to a solvent-free residue. The residue was distilled *in vacuo* to yield the products tabulated in Table I.

Preparation of substituted 2-pyridylamino ethanols (Table II). The indicated quantities of 2-bromopyridine and the appropriate aminoalcohol were heated in an oil-bath, kept at the noted temperature or, when carried out in cumene, at the reflux temperature of the mixture for the indicated number of hours. After being allowed to cool, the mixture was dissolved in chloroform. The chloroform solution was shaken with sufficient saturated potassium carbonate solution to neutralize the hydrogen bromide formed in the reaction. The chloroform solution was dried over potassium carbonate, and evaporated to dryness. The residue was distilled *in vacuo* to yield the products listed in Table II.

Preparation of esters of the amino alcohols (Table III). Five grams of the amino alcohol was mixed with 5 ml. of benzoyl chloride (added in portions of 1 ml. with adequate stirring and chilling), 8 g. of *p*-nitrobenzoyl chloride, or 6.5–8 grams of diphenylacetyl chloride (7) in a heavy-walled test-tube with a stout stirring rod. The mixture was heated very gently on a steam-bath to start the reaction if it was not spontaneous. As soon as the vigorous exothermic reaction occurred, the test tube was immersed in an ice-bath and stirred vigorously. When the reaction was complete, the contents of the test-tube were transferred, with the aid of hot water, to a separatory funnel, made alkaline with strong squeous sodium hydroxide solution, and extracted with ether [In the case of N-(2-pyridyl)-diethanolamine and 2-methyl-2-(2[1]-pyridyl)amino-1,3-propanediol, the *p*-nitrobenzoates were insoluble in ether, so chloroform was used as the extracting agent]. The combined ether extracts were dried over potassium carbonate and the ether removed *in vacuo*. If the residue solidified, the product was recrystallized from the solvent indicated. If the product did not crystallize, it was purified through the picrate. The latter was prepared in anhydrous ether, recrystallized to constant melting point and the picrate decomposed with aqueous ethanolamine. This was accomplished by shaking the finely-powdered picrate with a mixture of ether and a concentrated ethanolamine solution in water. The ether solution was drawn off and the aqueous layer extracted 3 times more with ether. The ether extracts were combined and washed with aqueous ethanolamine solution till the latter was no longer colored yellow, then dried over potassium carbonate and the ether removed *in vacuo*. Some of the esters gave no solid salts, including picrates, and were analyzed and tested in the crude form after removal of the ether.

The *p*-nitrobenzoates were not purified but were reduced directly to the *p*-aminobenzoates. The residue left after removal of the ether was transferred to a hydrogenation bottle and suspended in 75–100 ml. of 95% ethanol. Two grams of 10% palladium-charcoal catalyst was added and the compound hydrogenated at 50–60 lbs. When the hydrogen uptake was complete, the catalyst was filtered off and the solvent removed *in vacuo*. The products were then worked up in the same manner as the other esters.

In order to favor esterification over amide formation, in the case of the secondary amino alcohols, the latter were converted to their hydrochlorides before esterification (8).

SUMMARY

The synthesis of a series of N-2-pyridylalkanolamines, and some esters derived from these alcohols is described. The synthesis of four new dialkylaminoalkylalkanolamines as intermediates in the above syntheses is described.

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[CONTRIBUTION #180 FROM THE RESEARCH LABORATORIES OF HOFFMANN-LA ROCHE, INC.]

1,3,4-TRISUBSTITUTED PIPERIDINE DERIVATIVES FROM MANNICH BASES

JOHN T. PLATI, ROBERT A. SCHMIDT, AND WILHELM WENNER

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In a previous communication (1) the Mannich reaction involving acetophenone, methylamine hydrochloride, and formaldehyde was discussed. From the reaction mixture β-benzoylethylmethylamine (IV) and bis-(β-benzoylethyl)-methylamine (VIII) could be isolated directly as hydrochlorides. It was shown that when either of these compounds was treated with alkali, a third cyclic compound (XV) could be obtained in excellent yield (1, 2).

In the course of our work it appeared desirable to prepare substantial quantities of other cyclic ketones of the general formula III. With this goal in mind the Mannich reaction was varied, first, by replacing methylamine with other primary amines and secondly, by replacing acetophenone with some of its phenyl-substituted derivatives. Table I lists the compounds prepared.

The condensation was brought about with alcohol as a solvent and in certain cases without a solvent. When no solvent was used, the reaction became extremely vigorous and was complete in a few minutes. Large scale runs might very well lead to uncontrollable reactions, and for this reason they are not recommended.

In the original reaction, when two moles of acetophenone, two moles of formaldehyde, and one mole of methylamine hydrochloride was used, the main product was the bis compound VIII. The monoketoneamine IV was obtained in much smaller amounts with difficulty. However, in two cases the situation was reversed. Despite the fact that two moles of acetophenone and two moles of formaldehyde were allowed to react with isopropylamine hydrochloride only the monoketoneamine V was isolated. It was obtained in a yield of 43% whereas the diketoneamine was not isolated at all. When this same ratio was used with benzylamine hydrochloride the monoketoneamine VI was obtained in about 50% yield.

Although the conversion of the hydrochloride of bis-(β-benzoylethyl)methylamine (VIII) into the piperidine base (XV) was proved earlier (1) beyond doubt, it was necessary to demonstrate that alkali would cause the same conversion of other diketoneamines of type II into piperidine derivatives. This isomerization was established in four other cases by the fact that in each case the melting point of the original diketoneamine hydrochloride is different from the melting point of the hydrochloride of the piperidine base, obtained by treatment with alkali. The isomeric pairs are listed horizontally in Table II along with their melting points.

When the hydrochlorides of type II are stirred with alkali, the bases thus precipitated are at first oily or gummy but they slowly solidify on prolonged

stirring. The minimum time required for maximum solidification varies with the compound and depends to a great degree on the efficiency of stirring.

The conversion of monoketoneamines of type I into III by means of alkali has already been discussed (1, 2) in the case of the N-methyl derivative (IV). The

TABLE I

LIST OF COMPOUNDS

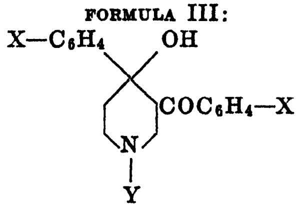
	DERIVATIVE	X	Y
FORMULA I: $X\text{-}C_6H_4COCH_2CH_2NH\text{-}Y$	IV	H	CH_3
	V	H	$CH(CH_3)_2$
	VI	H	$CH_2C_6H_5$
	VII	H	$n\text{-}C_4H_9$
FORMULA II: $(X\text{-}C_6H_4COCH_2CH_2)_2N\text{-}Y$	VIII	H	CH_3
	IX	$m\text{-}OCH_3$	CH_3
	X	$p\text{-}OCH_3$	CH_3
	XI	H	$n\text{-}C_4H_9$
	XII	p-Cl	CH_3
	XIII	$p\text{-}CH_3$	CH_3
	XIV	H	C_2H_5
FORMULA III: 	XV	H	CH_3
	XVI	H	$CH(CH_3)_2$
	XVII	H	$CH_2C_6H_5$
	XVIII	H	$n\text{-}C_4H_9$
	XIX	$m\text{-}OCH_3$	CH_3
	XX	p-Cl	CH_3
	XXI	$p\text{-}CH_3$	CH_3
	XXII	H	C_2H_5

TABLE II

MELTING POINTS OF HYDROCHLORIDES OF DIKETONEAMINES (II) AND PIPERIDINE DERIVATIVES (III)

DIKETONEAMINES		PIPERIDINE DERIVATIVES	
Hydrochloride of	M.P., °C	Hydrochloride of	M.P., °C
XI	77–80[a]	XVIII	182–184
XII	160–162	XX	192–193
XIII	159–160	XXI	195–197
XIV	138–139	XXII	206–208

[a] Contains solvent of crystallization.

reaction was now found to be quite general. Thus the N-isopropyl (V), the N-butyl (VII), and the N-benzyl (VI) derivatives undergo this reaction in the same way as the N-methyl derivative (IV). There is no doubt that the reaction involves decomposition into phenyl vinyl ketone and the primary amine, which recombine in a different ratio to give a base of type II, as first pointed out by Blicke and Burckhalter (2). The latter product then undergoes isomerization into III.

In the reaction of *m*-methoxyacetophenone with methylamine hydrochloride and formaldehyde in alcohol, it was not possible to isolate a product directly. Instead the alcohol was removed and the neutral organic matter was extracted with ether. Treatment of the residue with alkali liberated the organic bases which were quickly extracted with ether and converted into the oxalate. It is not likely that this short treatment with alkali was sufficient to convert the bis compound (IX) into the piperidine derivative XIX, so that we can presume that we are dealing with the oxalate of IX. Conversion of the oxalate into the piperidine base XIX was effected by prolonged treatment with alkali.

The situation was somewhat different with *p*-methoxyacetophenone. Here again it was not possible to isolate any product directly from the Mannich condensation. The base was converted into an oxalate and into a sulfate, which presumably are salts of X, since only a very short contact with alkali was allowed. However, in this case prolonged treatment with alkali did not result in the formation of a solid base in contrast to the behavior of the other ketoneamines reported in this paper.

Acknowledgment. We are indebted to Dr. A. Steyermark for microanalyses and to Mr. P. Bevilacqua for technical assistance.

EXPERIMENTAL

PART I. MONOKETONEAMINES—$XC_6H_4COCH_2CH_2NHY$

A. *β-Benzoylethylisopropylamine* (*V*). A mixture of 120 g. of acetophenone, 48 g. of iso propylamine hydrochloride, and 32 g. of paraformaldehyde was heated to 80° in a 2-liter beaker. After the initial vigorous reaction (1), 200 cc. of ethyl acetate was added and the mixture allowed to crystallize. A yield of 49 g. (43%) of the crude hydrochloride was obtained. Crystallization from ethanol gave the product melting at 174–176°.

Anal. Calc'd for $C_{12}H_{17}NO \cdot HCl$: C, 63.28; H, 7.97.

Found: C, 63.38; H, 7.86.

B. *β-Benzoylethylbenzylamine* (*VI*). The hydrochloride was prepared in 55% yield by Mannich and Hieronimus (3), who used equimolar amounts of reagents. The preparation was essentially repeated by us except that approximately two moles of acetophenone and two moles of formaldehyde were used with one mole of benzylamine hydrochloride. The monoketoneamine compound was obtained in approximately the same yield as that reported by Mannich and Hieronimus. Part of the product was converted into the *oxalate* which after crystallization from ethanol melted at 194–195°.

Anal. Calc'd for $C_{16}H_{17}NO \cdot C_2H_2O_4$: C, 65.64; H, 5.81; N, 4.25.

Found: C, 65.67; H, 5.39; N, 4.33.

C. *β-Benzoylethyl-n-butylamine* (*VII*). A mixture of 111 g. of acetophenone, 28 g. of paraformaldehyde, 50 g. of butylamine hydrochloride, and 250 cc. ethanol was refluxed with stirring for approximately two hours. The solvent was removed *in vacuo* below 60°, and the residue was stirred with 500 cc. of ether. The precipitated solid was filtered, and the filtrate was treated with more water and ether until after shaking two distinct phases were present. The ether phase was extracted several times with normal hydrochloric acid until the acid extract no longer gave a precipitate with sodium hydroxide. The combined aqueous phase and acidic extracts were made alkaline and the organic base extracted with ether. Addition of an ethereal solution of oxalic acid gave a crude compound which yielded 21 g. of the pure *oxalate* of β-benzoylethyl-*n*-butylamine, m.p. 177–179°, after crystallization from ethanol.

Anal. Calc'd for $C_{13}H_{19}NO \cdot C_2H_2O_4$: C, 61.00; H, 7.17; N, 4.74.

Found: C, 60.79; H, 6.99; N, 4.83.

PART II. DIKETONEAMINES—$(XC_6H_4COCH_2CH_2)_2NY$

A. *Bis-(β-benzoylethyl)-n-butylamine* (*XI*). A mixture of 55 g. of *n*-butylamine hydrochloride, 120 g. of acetophenone, and 30 g. of paraformaldehyde was treated as in Part I A. After the reaction the crude mixture was stirred for 1.5 hours with 700 cc. of water. The white precipitate was filtered and crystallized from ethyl acetate. The yield of crystalline hydrochloride, m.p. 77–80°, amounted to 42%. It contained solvent of crystallization.

Anal. Calc'd for $C_{22}H_{27}NO_2 \cdot HCl \cdot 1/2\ H_2O$: C, 69.00; H, 7.63.

Found: C, 68.85; H, 7.73.

B. *Bis-(β-m-methoxybenzoylethyl)methylamine* (*IX*). A mixture of 75 g. of *m*-methoxyacetophenone, 17 g. of methylamine hydrochloride, 15 g. of paraformaldehyde, and 80 cc. of ethanol was refluxed for two hours after which an additional 15 g. of paraformaldehyde was added. After 4.5 hours of refluxing the solvent was removed *in vacuo* and the residue was shaken with water and ether. The aqueous layer was separated, made alkaline, and the bases were extracted with ether. Addition of oxalic acid in ether gave the crude oxalate. After digestion with hot acetone and a hot filtration, it weighed 52 g. Crystallization from water gave the purified *oxalate*, m.p. 117–119° with sintering at 111°.

Anal. Calc'd for $C_{21}H_{25}NO_4 \cdot C_2H_2O_4$: Neut. equiv., 223. Found: Neut. equiv., 224.

C. *Bis-(β-p-methoxybenzoylethyl)methylamine* (*X*). By essentially the same method as in Part II B starting with *p*-methoxyacetophenone, a yield of 19% of the *oxalate*, m.p. 154–157° was obtained after a previous digestion with hot ethanol.

Anal. Calc'd for $C_{21}H_{25}NO_4 \cdot C_2H_2O_4$: Neut. equiv., 223. Found: Neut. equiv., 229.

When the base prepared from the oxalate was treated in ether with sulfuric acid, a *sulfate* was obtained. Crystallization from acetone yielded a product melting at 92–96°. Crystallization from water gave a product melting at 99–104° containing one molecule of water of crystallization.

Anal. Calc'd for $C_{21}H_{25}NO_4 \cdot H_2SO_4 \cdot H_2O$: C, 53.48; H, 6.20.

Found: C, 53.46; H, 6.07.

D. *Bis-(β-p-chlorobenzoylethyl)methylamine* (*XII*). The preparation of this compound was carried out by the procedure described in Part I A, using *p*-chloroacetophenone instead of acetophenone. The crystalline cake was stirred with acetone to give an 82% yield of the *hydrochloride*. Crystallization from ethanol gave a product melting at 160–162°. The compound could not be purified satisfactorily.

Anal. Calc'd for $C_{19}H_{19}Cl_2NO_2 \cdot HCl$: C, 56.94; H, 5.03.

Found: C, 57.78; H, 5.22.

E. *Bis-(β-p-toluylethyl)methylamine* (*XIII*). When 125 g. of *p*-methylacetophenone, 28 g. of paraformaldehyde, and 31 g. of methylamine hydrochloride were reacted in the manner described in Part I A, a crude hydrochloride was obtained, which on crystallization from ethanol gave a 38% yield of practically pure *hydrochloride* of m.p. 159–160°.

Anal. Calc'd for $C_{21}H_{25}NO_2 \cdot HCl$: C, 70.08; H, 7.28.

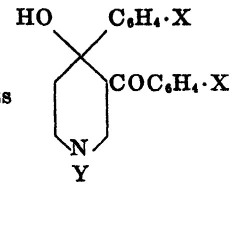
Found: C, 70.00; H, 7.34.

F. *Bis-(β-benzoylethyl)ethylamine* (*XIV*). The reaction of 120 g. of acetophenone, 20 g. of paraformaldehyde, and 41 g. of ethylamine hydrochloride according to Part I A yielded a crude *hydrochloride* which was crystallized from ethyl acetate and from ethanol. An 85% yield of material of m.p. 127–131° was obtained. Another crystallization from alcohol gave the pure compound of m.p. 138–139°.

Anal. Calc'd for $C_{20}H_{23}NO_2 \cdot HCl$: C, 69.45; H, 6.99.

Found: C, 69.73; H, 6.75.

PART III. PIPERIDINES



A. *1-Isopropyl-3-benzoyl-4-hydroxy-4-phenylpiperidine* (*XVI*). A suspension of 138 g. of crude β-benzoylethylisopropylamine hydrochloride (Part I A) was stirred for about an hour with 20 g. of sodium hydroxide and 1200 cc. of water and allowed to stand until solidification was complete. The solid was crystallized from methanol and acetone in a yield of 85%. The pure compound melts at 123–124°.

Anal. Calc'd for $C_{21}H_{25}NO_2$: C, 77.98; H, 7.79.

Found: C, 77.88; H, 7.65.

B. *1-Benzyl-3-benzoyl-4-hydroxy-4-phenylpiperidine* (*XVII*). β-benzoylethylbenzylamine hydrochloride was stirred for 4 hours at 50–60° with excess dilute sodium hydroxide. The crude base was crystallized from ethanol to give a 78% yield of the cyclic base. After crystallization from ethanol it melted at 116–119°. The compound was first isolated as a by-product by Mannich and Hieronimus (3) who reported approximately the same melting point.

Anal. Calc'd for $C_{25}H_{25}NO_2$: C, 80.83; H, 6.78; N, 3.77.

Found: C, 80.45; H, 6.81; N, 3.86.

The *hydrochloride*, prepared by passing hydrogen chloride gas through the ether solution of the base, melts at 193–194°.

C. *1-n-Butyl-3-benzoyl-4-hydroxy-4-phenylpiperidine* (*XVIII*). The crude mixture from Part II A was stirred with 30 g. of sodium hydroxide and 750 cc. of water for several hours. After standing overnight the crude base was crystallized from methanol to give a 50% yield of product melting at 94–96°. The pure product obtained by recrystallization from methanol melted at 97–99°.

Anal. Calc'd for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.07.

Found: C, 78.18; H, 7.65.

The same base was obtained when the oxalate of β-benzoylethylbutylamine (XI) from Part I C was stirred with alkali. The *hydrochloride* was crystallized from acetone; m.p. 182–184°.

Anal. Calc'd for $C_{22}H_{27}NO_2 \cdot HCl$: Cl, 9.49. Found: Cl, 9.36.

D. *1-Methyl-3-m-methoxybenzoyl-4-hydroxy-4-m-methoxyphenylpiperidine* (*XIX*). A mixture of 122 g. of bis-(β-*m*-methoxybenzoylethyl)methylamine oxalate from Part II B was stirred 2.5 hours with 20 g. of sodium hydroxide and 1200 cc. of water. After standing overnight the crude base was crystallized from dilute methanol in 90% yield. Recrystallization from methanol gave the pure compound, melting at 105–106°.

Anal. Calc'd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09.

Found: C, 71.47; H, 6.97.

E. *1-Methyl-3-p-chlorobenzoyl-4-hydroxy-4-p-chlorophenylpiperidine* (*XX*). To 100 cc. of boiling water was added with stirring 10 g. of bis-(β-chlorobenzoylethyl)methylamine hydrochloride and 30 cc. of 10% sodium hydroxide. The mixture was allowed to cool with stirring, and the crude base was crystallized from benzene. The yield of pure compound melting at 156–159° was 32%.

Anal. Calc'd for $C_{19}H_{19}Cl_2NO_2$: C, 62.64; H, 5.26.

Found: C, 62.39; H, 5.24.

The *hydrochloride* was crystallized from acetonitrile; m.p. 192–193°.

Anal. Calc'd for $C_{19}H_{19}Cl_2NO_2 \cdot HCl$: Cl (ionic), 8.86. Found: Cl, 8.78.

F. *1-Methyl-3-p-toluyl-4-hydroxy-4-p-tolylpiperidine* (*XXI*). A mixture of 67 g. of the bis-(β-*p*-toluylethyl)methylamine from Part II E, 10 g. of sodium hydroxide, and 540 cc. of water was stirred vigorously for an hour. After standing until solidification was complete, the crude base was crystallized from 70% ethanol; yield, 68%. Recrystallization from methanol gave crystals, melting at 140–143°.

Anal. Calc'd for $C_{21}H_{25}NO_2$: C, 77.98; H, 7.79.

Found: C, 78.01; H, 7.43.

The *hydrochloride* was crystallized from alcohol-ether; m.p. 195–197°.

Anal. Calc'd for $C_{21}H_{25}NO_2 \cdot HCl$: Cl, 9.87. Found: Cl, 9.66.

G. *1-Ethyl-3-benzoyl-4-hydroxy-4-phenylpiperidine* (*XXII*). A mixture of 147 g. of bis-(β-benzoylethyl)ethylamine (Part II F), 20 g. of sodium hydroxide, and 1200 cc. of water was stirred for 3 hours. After standing overnight and with additional stirring the base solidified;

it was crystallized from methanol or dilute methanol to give a 74% yield of the piperidine derivative. Recrystallization from acetone or dilute methanol gave a product melting at 100–102°.

Anal. Calc'd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49.

Found: C, 77.79; H, 7.09.

The *hydrochloride* was crystallized from ethanol, m.p. 206–208°.

Anal. Calc'd for $C_{20}H_{23}NO_2 \cdot HCl$: C, 69.45; H, 6.99.

Found: C, 69.60; H, 7.17.

SUMMARY

Mannich condensations between acetophenone and its ring substituted derivatives with formaldehyde and primary amines yield secondary and tertiary amines. Both products are converted by alkali into 1,3,4-trisubstituted piperidine derivatives.

NUTLEY, NEW JERSEY

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[COMMUNICATION No. 1200H FROM THE KODAK RESEARCH LABORATORIES]

THE STRUCTURE OF THE SOLID REACTION PRODUCT OF ANILINES AND ETHYL ORTHOFORMATE[1,2]

EDWARD B. KNOTT AND ROY A. JEFFREYS

Received May 2, 1949

Lewis, Krupp, Tieckelmann, and Post (1) have presented evidence based on cryoscopic molecular-weight determination in benzene to show that the solid reaction product of aniline or isomeric chloroanilines with ethyl orthoformate is trianilinomethane, or the analogous chloro derivatives, irrespective of the reaction temperature or of the molar ratio of the reactants. According to Walther (2), aniline and ethyl orthoformate, in the molar ratio of 2:1, condense at 100° to give diphenylformamidine (I; R = C_6H_5), m.p. 139°, whilst with a molar ratio of 3:1 and at reflux temperature, Giacolone (3) claims that trianilinomethane (II; R = C_6H_5), m.p. 139°, is formed. In most chemical reactions where the formation of isomers is excluded, it is usually possible to identify, or distinguish between, two possible reaction products by recourse to elementary analysis. In the present case, as pointed out by Lewis and co-workers, such analysis cannot be decisive. The percentages of carbon, hydrogen, and nitrogen in diphenylformamidine and trianilinomethane are so similar that the small differences come within the experimental error of their determination. However, the percentage chlorine found by Giacolone for the hydrochloride of the product shows that it is accurate for trianilinomethane monohydrochloride and cannot apply to diphenylformamidine hydrochloride. He finds similar agreement with analogs. Lewis and his co-workers (1) have shown by mixed melting point determination that the products of Walther and Giacolone are identical. It is therefore clear that in both cases we are dealing with the same compound.

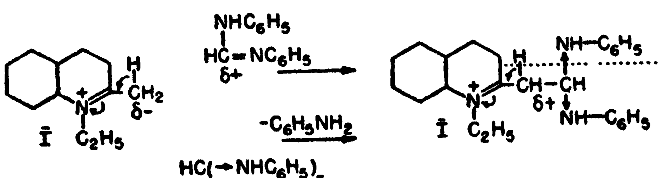
It has been generally accepted, hitherto, that the product is diphenylformamidine, and numerous patents and papers have been issued on the condensation of this substance with cyclic quaternary ammonium salts carrying a reactive methyl group (4) or with reactive keto-methylene compounds (5). Since this substance is of prime importance in the preparation of intermediates for photographic sensitizing dyes, it was thought desirable to prove, by unambiguous synthesis, its true structure.

Doubt as to the stability of a substance containing a carbon atom bonded to three secondary amino groups, as in trianilinomethane, was raised by the general instability of compounds containing a carbon bonded to two such groups. It is a general rule that the greater the number of electronegative atoms bonded to a carbon atom the more readily will the latter be attacked by nucleophilic reagents. The higher the electronegativity (−I effect) of the attached atoms,

[1] From the Research Laboratories, Kodak Ltd., Harrow, England.

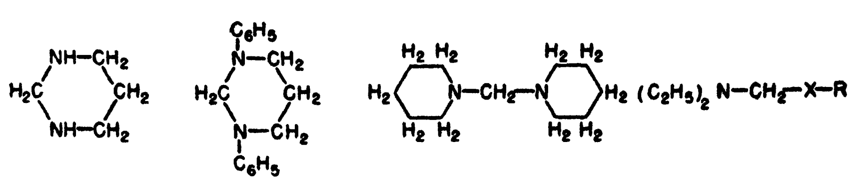
[2] Since this paper was written, Backer and Wanmaker (13) have shown by analysis of the picrate that the only solid reaction product of aniline and ethyl orthoformate is diphenylformamidine. In a later paper (14), they also showed by the same method that substituted anilines give only diarylformamidines.

the greater will be the carbon reactivity. This reactivity will, however, be tempered by any resonance stabilization present, or by any steric effects which will prevent a sufficiently close approach of the attacking nucleophilic center to the electrophilic carbon atom. Resonance stabilization is present only when the carbon atom carries a double bond. The state of electron deficiency at the carbon atom concerned may be relieved in three ways: through attack by a nucleophilic reagent, by intramolecular rearrangement, or by a spontaneous elimination reaction. The latter, however, can only occur if it results in a product of lower energy and thus higher stability. Thus, in general, it will occur most readily if, by elimination, an unsaturated resonating molecule results. Such elimination reactions are found most frequently when the molecule contains an active hydrogen atom which may be eliminated as a proton, together with one of the electronegative substituents carrying its charge to form two more stable products. Examples of such elimination reactions are manifold. An illustration of this effect in the field of the present paper is provided by the condensation of this solid reaction product with quinaldine ethiodide on fusion.



III

The quaternary salt carrying a nucleophilic 2-methyl carbon is attacked by the electrophilic methin carbon of diphenylformamidine or trianilinomethane. Carbon–carbon bond formation results as the proton is expelled from the reactive methyl group, the proton being taken up by the negative charge appearing on the anilonitrogen in one case or by the simultaneously expelled negative anilino ion in the other case. The intermediate, III, results. It also possesses a highly active β-carbon atom due to the electron drain from it. This electron deficiency is, at once, relieved by expulsion of an anilino group carrying its charge, together with a second proton from the α-methylene carbon which has been activated by hyperconjugative resonance. The resultant products, 2-β-anilinovinylquinoline ethiodide and aniline, are highly stable. Intermediates of Type III have never been isolated. The last step in the above reaction is dependent upon the presence in the molecule of an active hydrogen. In the absence of such active hydrogens, a certain degree of stability is obtained. Thus, whereas tetrahydropyrimidine (IV) has only been isolated as its N,N′-di-

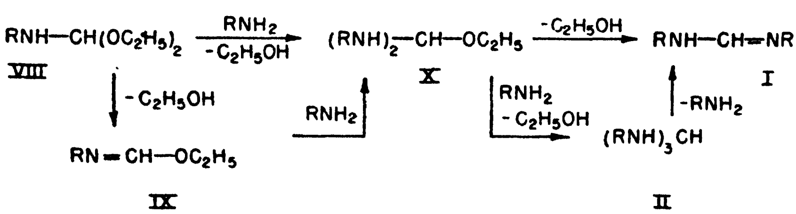


IV V VI VII

benzoyl derivative (6), the N,N′-diphenyl derivative (V) is stable (7). Similarly, open-chain derivatives of diaminomethane, such as VI, are relatively stable when compared with analogs derived from primary amines, but even VI is decomposed by water. Similarly, the diethylaminoethers and thioethers (VII) prepared by McLeod and Robinson (8) are stable to distillation but are attacked by water. The stability increases on replacing X = O by X = S, as would be expected from the lower electronegativity of sulfur compared with that of oxygen. Analogous compounds where R = H are extremely unstable.

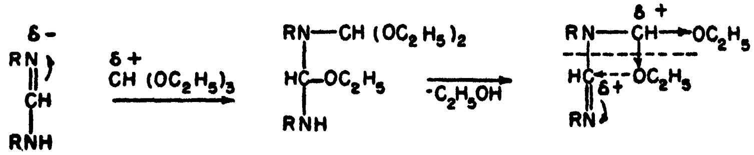
Returning to trianilinomethane containing three active N-hydrogens, we find that, by analogy, its instability would best be relieved by loss of aniline to give diphenylformamidine, the latter being stabilized somewhat by the weak resonance involving charge separation. The latter will, however, be highly stable in salt form, since proton addition will give an ion with two identical low-energy extreme resonance structures. It may, therefore, be stated that by analogy with other, related systems, one would expect the more stable end-product, diphenylformamidine, to be obtained from this reaction.

Before proceeding to the synthetic proof of the structure of the reaction product, a consideration of possible reaction mechanisms is desirable. Ethyl orthoformate contains a highly reactive electrophilic central carbon atom, owing to the strong −I effect of the three ethoxy groups. This atom is, however, protected from attack by the large effective size of the latter groups. It is considered, therefore, that for reaction with nucleophilic centers, such as amino nitrogen, the transition stage must be entered. Elimination of one molecule of alcohol will thus lead to the acetal (VIII). Goldschmidt (9) alleges that he isolated such an acetal when R = $CH_3OOC \cdot C_6H_4$, although it would be expected to have a very low order of stability. He gives no analytical figures and



scanty experimental details, including a wrong formula, and repetition of the experiment gave only the amidine. The next stage in the reaction may take two courses in order to relieve the instability of the central carbon atom. Either alcohol is eliminated to give the ethylisoformanilide (IX), or condensation with a further molecule of amine and elimination of alcohol gives the intermediate (X). The same intermediate may also result by addition of amine to IX. Indeed, Comstock and Kleeberg (10) have shown that ethylisoformanilide (IX; R = C_6H_5) reacts readily with aniline to give the solid product, m.p. 138°. X may then relieve its carbon instability by loss of alcohol to give the formamidine (I), or by further reaction with the amine to give the triaminomethane (II) and hence I by loss of amine.

Claisen (11) has shown that I (or II) reacts at high temperatures with ethyl orthoformate to give IX. The hypothetical intermediate (XI) will be highly



XI XII

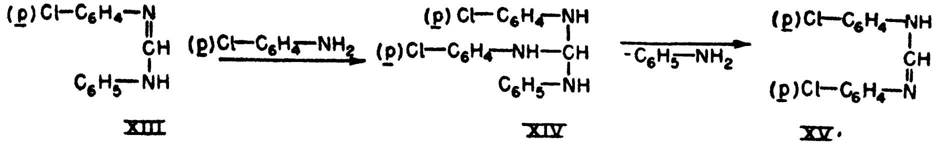
unstable and may decompose by loss of alcohol to give XII, which then relieves the electron drain from its two electrophilic carbons by migration of an ethoxy group and rupture of the C—N bond, as shown, giving two molecules of IX.

A consideration of the possible mechanism of the above reactions enables one to devise an unambiguous synthesis of diarylformamidines (I). The first step is to show that the reaction of one mole of arylamine with one mole of an ethylisoformanilide (IX; R = aryl) gives, by an addition-elimination reaction, an amidine (I) and not a triaminomethane (II). This was accomplished by condensing ethylisoformanilide (IX; R = C_6H_5) with *o*- and *p*-chloroaniline. Each resultant solid was homogeneous, and analysis showed each to contain one chlorophenyl and one phenyl residue: They must therefore be N-phenyl-N′-*o*-chlorophenylformamidine and the *p*-chloro isomer (XIII). The latter was obtained in nearly theoretical yield.

In an effort to induce a second chloroaniline molecule to add across the double bond of the amidine, ethylisoformanilide was heated with two moles of chloroaniline and the primary reaction product, the above amidine, was also heated with one mole of chloroaniline. When *o*-chloroaniline was employed, the identical unsymmetrical amidine was obtained or remained unchanged in the two cases. *p*-Chloroaniline, however, reacted with both isoanilide and amidine to give di-*p*-chlorophenylformamidine (XV), displacing the original anilo or anilino group. The identity of this compound as an amidine and not as tri-*p*-chloroanilinomethane was established by its resulting in theoretical yield from a molar mixture of ethyl-*p*-chloroisoformanilide and *p*-chloroaniline. Moreover, it was also identical (mixed m.p.) with the product obtained by Lewis and coworkers (1) from *p*-chloroaniline and ethyl orthoformate. Although the latter reports the m.p. 184° for this compound, we were not able to raise it above 181°, irrespective of the method of preparation.

These latter experiments are very pertinent to the arguments of this paper. Such a displacement of aniline was also reported by Walther (2), who obtained an unsymmetrical amidine on heating *p*-toluidine and diphenylformamidine. It implies at once that unsymmetrical trianilinomethanes are unstable since, in order to displace aniline, the *p*-chloroaniline must first add across the double bond of the unsymmetrical amidine (assumed to be the intermediate in the ethylisoformanilide reaction) to give anilinodi-*p*-chloroanilinomethane (XIV). This cannot be isolated, and the more electronegative group, anilino, is lost with a proton from a *p*-chloroanilino residue.

An unambiguous synthesis of diarylamidines having thus been established, ethylisoformanilide and aniline were reacted in molar proportions. The resultant



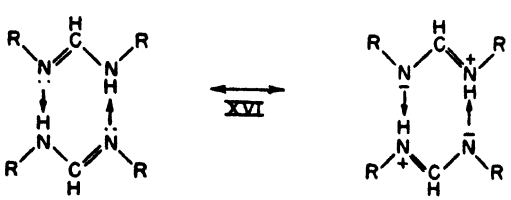
solid had m.p. 135° (crude), and the yield corresponded to a 99.5% recovery based on the loss of one mole of alcohol. One recrystallization gave a product of m.p. 139° and a recovery of 95%. The attempted addition of two moles of aniline to one of ethylisoformanilide gave the identical product, m.p. 139°, in a 94% yield based on the loss of one mole of alcohol and the utilization of only one mole of aniline. Both products gave a mixed m.p. of 139° with the products, m.p. 139°, obtained from ethyl orthoformate and aniline by the methods of Giacolone (3) and Walther (2).

Similarly, *o*-chloroaniline reacted with ethyl-*o*-chloroisoformanilide to give a solid, m.p. 140°, identical with the product obtained by Lewis and co-workers (1) from ethyl orthoformate and *o*-chloroaniline.

The foregoing affords conclusive synthetic proof that the only solid reaction product obtained from the interaction of arylamines and ethyl orthoformate is a diarylformamidine.

There remains to be explained the high molecular-weight figures obtained by Lewis and co-workers (1) and the low chlorine values obtained by Giacolone (3) for the hydrochlorides of his products.

The high molecular-weight figures may be due to intermolecular hydrogen-bonding (XVI). The resonance in the molecule will make this particularly facile. It would appear, therefore, to be fortuitous that the molecular weight



found, approximately one and one-half times that of the monomeric amidine, also corresponds to the molecular weight of the respective trianilinomethanes.

Since such bonding is likely to be weakened or lost at higher temperatures, the molecular weight of the product obtained by the method of Giacolone was determined by Rast's camphor procedure. The values found were 197 and 216, thus confirming the identity of the product with diphenylformamidine (molecular weight = 196).

Since triarylaminomethanes are not obtained by the method of Giacolone, then the analytical figures for chlorine in the hydrochlorides of his products are either incorrect or are meant to apply to the hydrochlorides of the tri-(*p*-aminophenyl)methanes which he obtained by heating his primary products with

aniline hydrochloride at elevated temperatures. To check these anomalies, diphenylformamidine hydrochloride was prepared by two methods: by passing hydrogen chloride into a benzene solution of the amidine (I) prepared according to Giacolone (3), and by mixing molar quantities of ethyl orthoformate, aniline, and aniline hydrochloride, according to the method of Claisen (11). The latter method gave a 94.5% yield of solid based on the loss of three moles of alcohol and must therefore be the required product. Both products, m.p. 245°, were identical and gave the correct chlorine figures.

For the sake of completeness, ethyl-*o*-chloroisoformanilide was condensed with *p*-chloroaniline to give N-*o*-chlorophenyl-N′-*p*-chlorophenylformamidine. It is interesting to note that the same unsymmetrical amidine is obtained from ethylisoformanilide and *o*-chloroaniline as from ethyl-*o*-chloroisoformanilide and aniline. This may confirm the intermediate formation of substances of Type X which then lose the more active N-hydrogen atom, this being the same in both cases. It may not confirm this, since the N-hydrogen in these amidines is probably highly mobile, as in imidazoles and benzimidazoles, so that separation of isomers is not possible.

Since aniline hydrochloride also rearranges substituted diarylformamidines to give symmetrically substituted tri-(*p*-aminophenyl)methanes (1, 3), it indicates that a chain of addition–replacement reactions must be involved.

EXPERIMENTAL[3]

Ethylisoformanilides. The method employed for the preparation of these reagents was essentially that of Claisen (11). The unsubstituted isoanilide was prepared by the inclusion of aniline hydrochloride, as recommended by Hamer, Rathbone, and Winton (12).

A mixture of 26.1 g. (0.2 mole) of *o*- or *p*-chloroaniline and 66 cc. (0.4 mole) of ethylorthoformate was heated in an oil-bath at 140° for two hours, when somewhat more than the calculated quantity of ethanol had distilled. This was contaminated with a little ethyl orthoformate. The product, an oil, was then distilled at atmospheric pressure. Ethyl-*o*-chloroisoformanilide was thus obtained as a colorless oil, b.p. 238–240° (769 mm.). Ethyl-*p*-chloroisoformanilide formed a colorless oil, b.p. 154° (45 mm.). In the preparation of the latter, a large quantity of di-*p*-chlorophenylformamidine was also obtained.

Anal. Calc'd for $C_9H_{10}ClNO$: Cl, 19.35.

Found: Cl, 19.1 (*o*-isomer); Cl, 19.2 (*p*-isomer).

Diphenylformamidine. (a) A mixture of 4.97 g. (0.033 mole) of ethylisoformanilide and 3.1 g. (0.033 mole) of aniline was heated for two hours on the steam-bath under slightly reduced pressure. The required amount of alcohol had then distilled. The solid product was ground under ligroin-benzene (2:1), collected, and dried. It had m.p. 135° and weighed 6.5 g. (99.5%). Recrystallized from benzene-ligroin, it formed colorless needles, m.p. 139°, in 94% yield.

(b) Proceeding as for (a) but using 6.2 g. (0.067 mole) of aniline and heating for three hours, the product obtained after washing out excess aniline with benzene-ligroin (1,2) had m.p. 139° [mixed m.p. with product from (a), 139°], yield, 94%.

N-Phenyl-N′-o-chlorophenylformamidine. (a) A mixture of 24.8 g. (0.166 mole) of ethylisoformanilide and 21.7 g. (0.166 mole) of *o*-chloroaniline was heated together on the steam-bath under slightly reduced pressure for two hours. The solid obtained on cooling weighed 26 g. (73%) and had m.p. 113° after having been washed with a little methanol. From the latter solvent it formed colorless tablets, m.p. 113°.

[3] Microanalyses were made by Drs. Weiler and Strauss, Oxford University, England.

(b) A mixture of 4.6 g. of ethyl-*o*-chloroisoformanilide and 2.3 g. of aniline treated as above gave the same product, m.p. 113°; the mixed melting point with the product obtained under (a) was 113°.

Anal. Calc'd for $C_{13}H_{11}ClN_2$: Cl, 15.4. Found: Cl, 15.49.

Heating ethylisoformanilide with two moles of *o*-chloroaniline on the steam-bath for three hours gave the same product, m.p. 113° [mixed m.p. with (a) and (b), 113°].

N-Phenyl-N'-p-chlorophenylformamidine. A mixture of 24.8 g. (0.166 mole) of ethylisoformanilide and 21.7 g. (0.166 mole) of *p*-chloroaniline was heated as for the *o*-isomer, giving a 100% yield of amidine. It formed colorless prisms, m.p. 122°, from methanol.

Anal. Calc'd for $C_{13}H_{11}ClN_2$: Cl, 15.4. Found: Cl, 15.1.

On employing two moles of *p*-chloroaniline for one mole of ethylisoformanilide, di-*p*-chlorophenylformamidine, m.p. 181°, was obtained in 62% yield. Mixed m.p. 181° with product obtained according to Lewis and co-workers (1) who record m.p. 184°.

N-o-Chlorophenyl-N'-p-chlorophenylformamidine. This amidine was readily obtained on heating molar quantities of *p*-chloroaniline and ethyl-*o*-chloroisoformanilide. It formed short, glassy needles, m.p. 155–159°, from methanol.

Anal. Calc'd for $C_{13}H_{10}Cl_2N_2$: Cl, 26.8. Found: Cl, 26.9.

Di-o-chlorophenylformamidine, m.p. 140°, was obtained in 80% yield from molar amounts of ethyl-*o*-chloroisoformanilide and *o*-chloroaniline. The melting point of 140° showed no depression on admixture with a specimen prepared according to Lewis and co-workers (1). The *p*-isomer, similarly prepared in 100% yield, had m.p. 181° and did not depress the melting point of a specimen prepared according to Lewis and co-workers (1). It was also obtained in 80% yield by fusing molar quantities of N-*p*-chlorophenyl-N'-phenylformamidine and *p*-chloroaniline on the steam-bath for one hour.

Anal. Calc'd for $C_{13}H_{10}Cl_2N_2$: Cl, 26.8. Found: Cl, 26.7.

Diphenylformamidine hydrochloride. (a) The base, prepared by the method of Giacolone, was treated in benzene solution with a stream of dry hydrogen chloride and the resultant precipitate recrystallized by the slow addition of ether to a warm methanol solution of the salt, giving glistening platelets, m.p. 245°, containing alcohol lost on heating for three hours at 100° and 20 mm.

Anal. Calc'd for $C_{13}H_{13}ClN_2$: Cl, 15.25. Found: Cl, 15.0.

(b) To a solution of 9.3 g. of aniline and 12.95 g. of aniline hydrochloride in 20 cc. of warm methanol was added 14.8 g. of ethyl orthoformate. A crystalline precipitate formed rapidly. After warming gently for five minutes, the reaction was complete and the required hydrochloride was completely precipitated by the addition of ether. After one recrystallization from methanol-ether, it was obtained in 94.5% yield, m.p. 245°. The mixed melting point with product obtained under (a) was 245°.

Anal. Calc'd for $C_{13}H_{13}ClN_2$: Cl, 15.25. Found: Cl, 15.1.

SUMMARY

1. Contrary to the conclusions of Giacolone (3), and of Lewis and his co-workers (1), it has been proved that the only solid reaction product of aniline and ethyl orthoformate is diphenylformamidine.

2. Analogous products were obtained when aniline was replaced by *o*- or *p*-chloroaniline.

3. Unsymmetrical chloro derivatives of diphenylformamidines were prepared.

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OXAZOLINES

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β-Hydroxyalkylamides have been converted to oxazolines by such agents as heat, sulfuric acid, phosphorus pentoxide, phosphorus pentachloride, and thionyl chloride. Bergmann, *et al.*, developed the use of thionyl chloride but did not take into account the rearrangement of oxazoline hydrochlorides into β-chloroalkylamides (1, 2). This rearrangement is known and has been correlated with the similar degradation of imino-ether hydrochlorides to alkyl chlorides and amides (3, 4). The accidental discovery in this laboratory that the compound described as 2-phenyl-4-carboxymethyloxazoline hydrochloride (1) is methyl α-benzoylamino-β-chloropropionate led to a re-examination of this reaction to see whether ring closure involves the chlorosulfinate or the chloro derivative, the amide group or a derivative thereof, and whether thionyl chloride is necessary as a condensing medium.

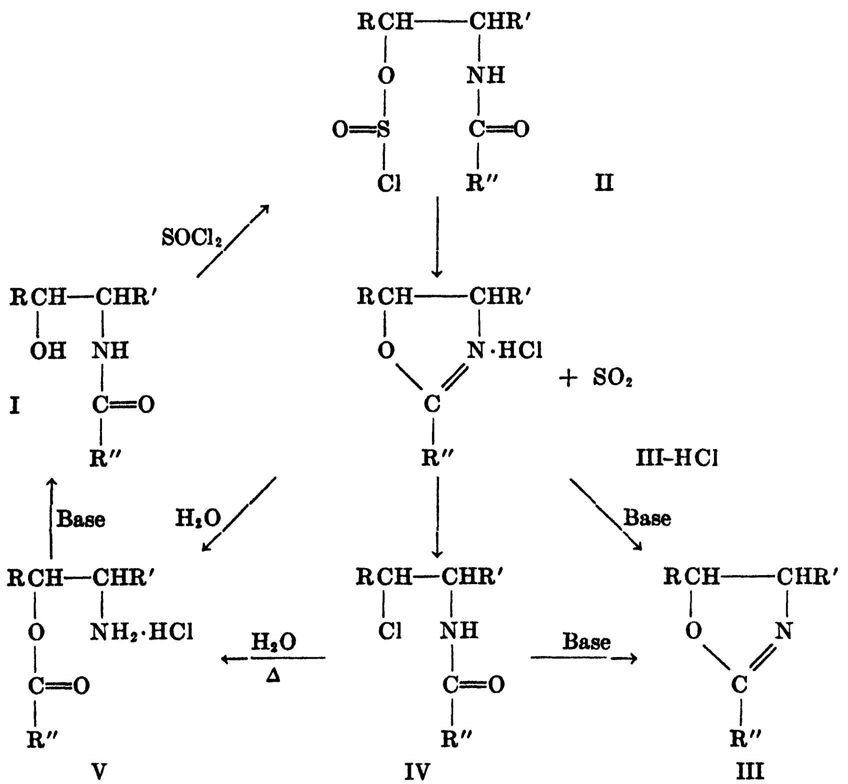
β-Chloroalkylamides seem inert to thionyl chloride and are therefore eliminated as intermediates in the formation of oxazolines. Recovered as end product, the β-chloroalkylamides can arise either from direct replacement of hydroxyl by chlorine or by transformation of the oxazoline salt. Although simple primary and secondary alcohols give stable chlorosulfinates (5), the presence of amide hydrochloride might lead to replacement by chlorine in a manner analogous to the catalytic effect of amine salts (6). But in no case has a β-chloroalkylamide been recovered when the reaction mixture is kept cold, whereas it appears to be the only product when refluxing thionyl chloride is used. That the oxazoline is the intermediate in all but one of the cases cited in the experimental section was shown by isolating either the oxazoline or its hydrolysis product, the β-aminoalkylester hydrochloride. In the exceptional case, the product formed from β-hydroxyethylformamide and thionyl chloride is a crystalline solid showing the combined weight of the reactants. Oxazoline was not proved to be one of its components on decomposition with alkali, but on heating it yielded β-chloroethylformamide as reported by Wenker for the product obtained with thionyl chloride on the steam-bath (7).

Leffler and Adams used refluxing thionyl chloride to get "dihydrochlorides" of amine-substituted oxazolines which were not characterized but were decomposed in sodium hydroxide to yield the oxazolines (8). A repetition of one of the preparations showed that the oxazoline resulted from ring closure of the β-chloroalkylamide rather than from oxazoline salt decomposition.

The chart shows the relationships involved and is known to be valid in its entirety for at least one of the systems examined. The chlorosulfinate (II) was identified by its reaction products. It reverted to the original β-hydroxyalkylamide on hydrolysis and condensed with the latter to give a sulfite ester. The chlorosulfinate expelled sulfur dioxide on heating, to give the oxazoline hydro-

chloride (III-HCl), which rearranged to the amide (IV) on further heating. Thus, thionyl chloride did not participate in oxazoline formation. It is possible that the oxazoline salt is formed in all cases but is not attainable if the energy required to form it is more than that needed in its rearrangement to the β-chloroalkylamide (IV).

The possibility of confusing III-HCl and IV is made evident by their physical and chemical similarity. The melting piont of III-HCl may not be observable as more than a slight sinter as it passes into and melts as IV. Both are transformed into the same compound in aqueous solutions. Hydrolysis of the oxazoline salt may take place more easily than the transformation of IV to V (probably *via* III-HCl), and under alkaline conditions base liberation is more rapid than ring closure of IV to III, but the differences are ones of degree and the mistaken identity in the Bergmann papers (1) seems to be the origin of the idea that oxazoline salts are only slowly hydrolyzed by boiling water (8). Some salts are rapidly hydrolyzed at room temperature, but no example was found in which hydrolysis



took more than two-minutes heating on the steam-bath. Since hydrolysis and formation of the β-haloalkylamide involve anionic attack on positions two and five, a high concentration of halide ion should favor the formation of the β-haloalkylamide. Thus, Gabriel and Heymann (9) obtained a high yield of β-chloroethylbenzamide by the action of hydrochloric acid on 2-phenyloxazoline

hydrochloride, whereas the action of hot water on this salt is primarily one of hydrolysis with the amide as secondary product. Under these conditions the existence of the β-chlorobenzamide is, of course, transitory.

EXPERIMENTAL

PART 1: R = H, R′ = $COOCH_3$ or COOH, R″ = C_6H_5

Transformation of N-benzoyl-DL-serine methyl ester (I) to methyl α-benzoylamino-β-chloropropionate (IV).[1] The starting material was prepared according to Bergmann and Miekeley (1) and the oily ester or an ethereal solution of the ester treated cold with a 4- to 8-fold excess of thionyl chloride. The crystalline product was a complex salt containing sulfur dioxide in the approximate ratio of 1 mole of sulfur dioxide to 2.1 moles of base. It sintered at about 57°, resolidified and melted at 108–112°. The salt seemed stable cold but at room temperature and more rapidly on warming, it lost sulfur dioxide and also its water solubility to give methyl α-benzoylamino-β-chloropropionate (IV). That the sulfur dioxide was bound alone with hydrogen chloride in a salt and not in the intermediate chlorosulfinate was indicated by the high yield of O-benzoylserine methyl ester hydrochloride (V) on hydrolysis (see below), and by the fact that a mixture of hydrogen chloride and sulfur dioxide bubbled through an ethereal solution of 2-phenyl-4-carboxymethyl-oxazoline (III) gave a similar salt containing less sulfur dioxide; it decomposed on heating to give sulfur dioxide in a ratio of 1 mole to 3.4 moles of methyl α-benzoylamino-β-chloropropionate (IV).

Methyl α-benzoylamino-β-chloropropionate (IV), m.p. 114–116°, was obtained in 86% yield when the reaction was run at the reflux temperature of ether for one hour. It was purified by adding water to a solution in hot alcohol. Bergmann and Miekeley (1) reported 113–114° as the melting point of 2-phenyl-4-carboxymethyloxazoline hydrochloride, and the value 117° has been given (10).

Anal. Calc'd for $C_{11}H_{12}ClNO_3$: C, 54.67; H, 5.00.
Found: C, 54.62; H, 4.86.

On heating in water this compound gave O-benzoylserine methyl ester hydrochloride (V) in 79% yield. It (IV) was unaffected by standing in ether-thionyl chloride (equal vols.) for two hours.

O-*Benzoylserine methyl ester hydrochloride (V)*, m.p. 137–138° (gas), was formed in 73% yield when the complex salt described above was dissolved in water. It was purified by dissolving in alcohol, then adding ether. Bergmann, *et al.*, (1) reported 130–132°.

Anal. Calc'd for $C_{11}H_{14}ClNO_4$: C, 50.87; H, 5.43.
Found: C, 50.89; H, 5.57.

2-Phenyl-4-carboxymethyloxazoline (III) was obtained in 72% yield when the complex salt described above was decomposed in sodium carbonate solution. It distilled at 133–135° (2 mm.), f.p. 29.5°, n^{23}_{D} 1.5501. The values 130–132° (0.4 mm.), and $n^{20.5}_{D}$ 1.5504 have been reported (1).

Anal. Calc'd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40.
Found: C, 64.39; H, 5.42.

O-Benzoylserine. 2-Phenyl-4-carboxymethyloxazoline (III) dissolved in 2 *N* sodium hydroxide to give a crystalline, acetone-insoluble sodium salt. A solution of the salt with an equivalent amount of hydrochloric acid gave 2-phenyl-4-carboxyoxazoline (III), m.p. 159–161°; previously reported (1) m.p. 159–160°. It was purified by dissolving in acetone and concentrating the hot solution. This substance hydrolyzed at room temperature in 95% alcohol solution to give O-benzoylserine (V) in 96% yield, m.p. 145–145.5° (dec.), purified from water. The value 149–150° has been given (1).

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[1] Since all compounds were DL-forms, this designation will be omitted henceforth.

Anal. Calc'd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30.
Found: C, 57.60; H, 5.30.

O-Benzoylserine in sodium carbonate solution rearranged to *N-benzoylserine* in 91% yield.

α-Benzoylamino-β-chloropropionic acid (IV). When dry hydrogen chloride was passed into a solution of 2-phenyl-4-carboxyoxazoline (III) in dry dioxane a crystalline salt formed which dissolved on heating on the steam-bath for ten minutes. Removal of the solvent and addition of water gave crystalline α-benzoylamino-β-chloropropionic acid, m.p. 145–147°, in 86% yield.

Anal. Calc'd for $C_{10}H_{10}ClNO_3$: C, 52.76; H, 4.43.
Found: C, 53.00; H, 4.55.

This compound gives an 83% yield of O-benzoylserine (V) by first heating with water and then treating the hydrochloride solution with pyridine.

α-Benzoylaminoacrylic acid. Both α-benzoylamino-β-chloropropionic acid (IV) and its methyl ester gave α-benzoylaminoacrylic acid on treatment with 2 *N* sodium hydroxide at room temperature. The product was recovered on acidification and was purified by adding water to a solution in hot alcohol, m.p. 153–155° (gas and orange color); yield 72% from the ester. The previously reported melting point (11) was 137–138°.

Anal. Calc'd for $C_{10}H_9NO_3$: C, 62.82; H, 4.74.
Found: C, 62.58; H, 4.71.

This compound in alcohol solution absorbed hydrogen in the presence of Adams catalyst to give DL-*benzoylalanine*, m.p. 163–165°. The melting point was not depressed on mixing it with an authentic sample.

Anal. Calc'd for $C_{10}H_{11}NO_3$: C, 62.16; H, 5.74.
Found: C, 62.06; H, 5.86.

α-Benzoylamino-β-chloropropionic acid (IV) was converted to 2-phenyl-4-carboxyoxazoline (III) in approximately 50% yield by holding it in a sodium bicarbonate solution at 40° for 22 hours, then carefully liberating the product with hydrochloric acid.

PART 2: R = R′ = R″ = H

The product of the addition of twice the theoretical amount of thionyl chloride to hydroxyethylformamide (temperature not over 18°) was a crystalline solid. It was brought to constant weight after drawing the excess thionyl chloride off at 10 mm. while chilling in an ice-bath. This weight corresponded to approximately 94% of that required for the union of 1 mole of hydroxyethylformamide and 1 mole of thionyl chloride. The reverse addition did not give a solid due perhaps to the loss of hydrogen chloride. Attempts to decompose the compound in such a way as to get oxazoline were unsuccessful. A small amount of material boiling in the right range was isolated but gave poor analytical values. The solid, layered with dry ether, and put on the steam-bath, melted in a few minutes. After six hours it was distilled several times to give a 35% yield of β-chloroethylformamide, b.p. 118.5–121° (10 mm.), n_D^{25} 1.4845. This compound did not appear to be as unstable as previously reported, but in like manner gave poor analytical values (7).

Anal. Calc'd for C_3H_6ClNO: C, 33.50; H, 5.62; Cl, 32.97.
Found: C, 32.61; H, 5.47; Cl, 31.56.

PART 3: R = R′ = H; R″ = C_6H_5

Ethanolamine was benzoylated in sodium bicarbonate solution at 15°. The product was taken into chloroform, recovered, and distilled at 179–189° (1 mm.). The crude product (85% yield) was recrystallized by dissolving in warm ethyl acetate, then adding dry ether; m.p. 61–63°, 64% yield. It was previously reported (12) distilling at 185–187° (1 mm.), m.p. 60–61°.

2-Phenyloxazoline hydrochloride (III-HCl). β-Hydroxyethylbenzamide (2.0 g.) was added portionwise to 4 ml. of chilled thionyl chloride at not over 18°. The solution was kept

in the ice-bath for one hour; excess thionyl chloride was then removed under reduced pressure and the crystalline product brought to constant weight (2.3 g.) while keeping cold. The theoretical weight for the oxazoline hydrochloride is 2.22 g. The salt melted at 101–103° with a slight sinter at 77°. It was decomposed with sodium carbonate solution, the base removed with ether and the carbonate solution analyzed for sulfite and chloride ions. The ratio of the moles of sulfur dioxide to that of starting material was 0.03 to 1.0. Chloride was found in small excess, 105 % of theory. As reported (4) the oxazoline hydrochloride is stable in solution at room temperature. Recrystallization was effected by adding acetone to an aqueous solution; m.p. 75–76°. The value previously given (4) is 80–81°, and it is possible the lower melting point and low analytical value are due to loss of hydrogen chloride. The phenomenon of slight sintering at the melting point with transformation into *β-chloroethylbenzamide*, m.p. 101–103°, (see above) was observed solely with the crude reaction product.

Anal. Calc'd for $C_9H_{10}ClNO$: Cl, 19.31. Found: Cl, 18.46.

β-Aminoethyl benzoate hydrochloride (V), 0.133 g., m.p. 142–145°, and *β-chloroethylbenzamide (IV)*, 0.025 g., m.p. 99–101°, were recovered when 0.20 g. of 2-phenyloxazoline hydrochloride in aqueous solution was held on the steam-bath for two minutes. The identities were established after further purification by mixed melting points. The isolation of the latter compound shows that rearrangement can precede hydrolysis.

β-Chloroethylbenzamide (IV) was obtained by rearrangement of the oxazoline hydrochloride on the steam-bath. After purification from alcohol it was obtained in 88% yield, m.p. 102–103.5°. The literature gives values of 106–108° (4) and 102–103° (3).

Anal. Calc'd for C_9H_{10} ClNO: Cl, 19.31. Found: Cl, 19.78.

β-Aminoethyl benzoate hydrochloride (V). β-Chloroethylbenzamide (IV) 0.20 g., was covered with water and put on the steam-bath. The solid melted and the oil dissolved in the water in ten minutes. The water was removed and the crystalline product recovered from acetone in which it is insoluble. Yield, 0.193 g. (88%); m.p. 143–145°. The compound was purified by adding acetone to a solution in hot alcohol. The melting point was unchanged. The previoulsy reported (4) melting point is 129–130°.

Anal. Calc'd for $C_9H_{12}ClNO$: Cl, 17.58. Found: Cl, 17.54.

β-Aminoethyl benzoate hydrochloride (V) on rearrangement in a slight excess of sodium hydroxide solution gave β-hydroxyethylbenzamide (I) in 61% of theory.

PART 4: $R = ClCH_2$; $R' = H$; $R'' = p\text{-}NO_2C_6H_4$

3-Chloro-2-hydroxy-*n*-propylamine hydrochloride, m.p. 100–103°, was obtained in 15% yield, based on epichlorohydrin, by the method of Gabriel and Hohle (13). Reaction with *p*-nitrobenzoyl chloride in a benzene-layered sodium bicarbonate solution gave N-(3-chloro-2-hydroxy-*n*-propyl)-*p*-nitrobenzamide. Purified by adding benzene to a hot ethyl acetate solution, it melted 103–106°; yield 74%. The reported value (8) is 110–111°.

Anal. Calc'd for $C_{10}H_{11}ClN_2O_4$: C, 46.43; H, 4.29.

Found: C, 46.69; H, 4.49.

2-(3-Chloro-1-p-nitrobenzoylamino-n-propyl) chlorosulfinate (II). N-(3-Chloro-2-hydroxy-*n*-propyl)-*p*-nitrobenzamide (I) 2.0 g., was added to 3.0 ml. of thionyl chloride at not over 8°. Crystals rapidly formed. After standing in the ice-bath for 40 min., excess thionyl chloride was removed under reduced pressure and the product brought to constant weight while still in the ice-bath. The weight of the product was 2.65 g. with 2.64 g. theoretical for the chlorosulfinate. Decomposition with cold water yielded 1.81 g. (90%) of starting material, m.p. 100–103°, identity confirmed by a mixed melting point. Analysis of the aqueous mother liquor for chloride gave silver chloride in 96% of theory.

Di-2-(3-chloro-1-p-nitrobenzoylamino-n-propyl) sulfinate. In a similar run the chlorosulfinate was dissolved in a little dry dioxane and an equivalent amount of N-(3-chloro-2-hydroxy-*n*-propyl)-*p*-nitrobenzamide added. Removal of the solvent gave an oil which crystallized. The compound was purified by dissolving in pyridine (not over 100°) and then adding alcohol. The yield was 30%; m.p. 167–168° (gas).

Anal. Calc'd for $C_{20}H_{20}Cl_2N_4O_9S$: C, 42.64; H, 3.58; Cl, 12.59; S, 5.69.
Found: C, 42.90; H, 3.94; Cl, 12.24; S, 5.8.

2-(3-Chloro-1-amino-n-propyl) p-nitrobenzoate hydrochloride (*V*). The chlorosulfinate (II), 0.657 g., in a test tube connected with a sodium carbonate absorption solution was placed in steam for 4 min. It part. melted and the tube was swept with nitrogen. The loss of weight was 0.116 g. with 0.121 theory for loss of sulfur dioxide in ring closure to the oxazoline hydrochloride. Titration of the sodium carbonate solution with 0.1 *N* iodine solution showed sulfite ion in 86% of theory. The carbonate solution also gave chloride in molal quantity equivalent to 2% of the starting material. Eight ml. of water was added to the organic residue and the suspension warmed 2 min. on the steam-bath. After cooling, undissolved solid was filtered; yield, 0.145 g., m.p. 95–100°. This is impure N-(2,3-dichloro-*n*-propyl)-*p*-nitrobenzamide (IV) in 27% of theory. The remainder of the material, 2-(3-chloro-1-amino-*n*-propyl) *p*-nitrobenzoate hydrochloride (V), recovered from water and washed in acetone, melted at 184–186°; yield, 0.415 g. (73%). It was purified from alcohol and melted at 185–187° (gas).

Anal. Calc'd for $C_{10}H_{12}Cl_2N_2O_4$: C, 40.69; H, 4.10; Cl, 24.03.
Found: C, 40.90; H, 4.30; Cl, 23.70.

The benzoate (V) dissolved in water and treated with sodium bicarbonate solution threw down an oil which soon crystallized. It was purified to give N-(3-chloro-2-hydroxy-*n*-propyl)-*p*-nitrobenzamide (I) in 57% yield.

2-p-Nitrophenyl-5-chloromethyloxazoline (*III*). In another experiment the thionyl chloride suspension of the chlorosulfinate (II) was held on the steam-bath for 5 min., during which time the solid dissolved giving a clear solution. The thionyl chloride was removed under reduced pressure and the product crystallized easily when rubbed with a little dry ether. It weighed 2.14 g. with 2.15 g. being theoretical for the oxazoline hydrochloride, m.p. 127–129°. This salt is not very soluble in water and the base could be liberated by titrating with 2 *N* sodium hydroxide using phenolphthalein indicator. The impure oxazoline, m.p. 111–114°, recovered in 95% yield, was purified from alcohol; m.p. 116–117°, slight sinter at 113°. The literature (8) gives m.p. 117–118°.

Anal. Calc'd for $C_{10}H_9ClN_2O_3$: Cl, 14.73. Found: Cl, 14.68.

After standing in the air for several days, the oxazoline hydrochloride was found to have lost some hydrogen chloride to give the oxazoline, easily separated by reason of its acetone solubility.

N-(*2,3-Dichloro-n-propyl)-p-nitrobenzamide* (*IV*) resulted when the oxazoline hydrochloride alone or in thionyl chloride was rearranged by heating. Purified by adding water to a hot alcohol solution it melted at 122–123.5°. A mixture melting point with the oxazoline hydrochloride, m.p. 127–129°, showed a sharp depression, mixture m.p. 115–125°.

Anal. Calc'd for $C_{10}H_{10}Cl_2N_2O_3$: C, 43.34; H, 3.64.
Found: C, 43.52; H, 3.78.

The transformation of this compound (IV) into 2-(3-chloro-1-amino-*n*-propyl) *p*-nitrobenzoate (V) could not be effected by heating it in aqueous suspension for 24 hours on the steam-bath. In suspension in 2 *N* sodium methoxide it (IV) slowly cyclized to 2-*p*-nitrophenyl-5-chloromethyloxazoline (III).

PART 5: $R = HCl(C_2H_5)_2NCH_2$; $R' = H$; $R'' = p\text{-}NO_2C_6H_4$

N-(3-Diethylamino-2-hydroxy-n-propyl)-p-nitrobenzamide hydrochloride was made by heating N-(3-chloro-2-hydroxy-*n*-propyl)-*p*-nitrobenzamide with diethyl amine, twice theory, in a sealed tube on the steam-bath for one hour. The product was treated with excess absolute alcoholic hydrogen chloride to make the salt which was purified from absolute ethanol. Yield 75%; m.p. 162–163.5°. The reported melting point (8) is 163–164.5°.

2-(3-Diethylamino-1-amino-n-propyl) p-nitrobenzoate dihydrochloride (*V*). N-(3-Diethylamino-2-hydroxy-*n*-propyl)-*p*-nitrobenzamide hydrochloride (I), 0.30 g., with 1.0 ml. thionyl chloride gave a solution at room temperature. At the end of 20 minutes excess

thionyl chloride was removed under reduced pressure and 2 ml. of water added to the oil to give a solution. After removing the water under reduced pressure and adding acetone, a crystalline product was obtained which was purified by slowly adding acetone, to its solution in a little water. Yield, 0.065 g. (20%); m.p. 194–195° (gas).

Anal. Calc'd for $C_{14}H_{23}Cl_2N_3O_4$: Cl, 19.25. Found: Cl, 19.42.

N-(3-Diethylamino-2-chloro-n-propyl)-p-nitrobenzamide hydrochloride (IV) was obtained in 87% yield by rearrangement of 2-*p*-nitrophenyl-5-diethylaminomethyloxazoline dihydrochloride (III-HCl) on the steam-bath. It was also obtained in good yield by the action of hot thionyl chloride on N-(3-diethylamino-2-hydroxy-*n*-propyl)-*p*-nitrobenzamide (I). This compound (IV) has been designated the oxazoline dihydrochloride but was not characterized (8). It was purified by adding ethyl acetate to a solution in hot alcohol, m.p. 112.5–114.5°.

Anal. Calc'd for $C_{14}H_{21}Cl_2N_3O_3 \cdot H_2O$: Cl, ionic, 9.63; Cl, total, 19.26.
Found: Cl, ionic, 11.04; Cl, total, 19.39.

The high ionic chlorine is probably due to partial splitting off of the bound chlorine. The attempt to convert this compound to the ester (V) was inconclusive.

The oxazoline dihydrochloride (III-HCl) mentioned above was made by adding dry hydrogen chloride to a dry ethereal solution of the base. This base (III) was made as previously described (8) and melted at 55–57° [L. and A. (8) reported m.p. 57–57.5°] after purification from petroleum ether.

The *ease of hydrolysis* of the oxazoline dihydrochloride is illustrated by the following experiment: 2-*p*-nitrophenyl-5-diethylaminomethyloxazoline (III), 0.50 g., was slowly titrated with 1.0 *N* HCl. At one equivalent of acid (1.8 ml.) the solid was in complete solution, *p*H 7 by Accutint paper. Further addition of acid to two equivalents (3.6 cc.) was accompanied by an increase of *p*H to a value of 1 at the end. The water was immediately removed under reduced pressure at room temperature. Addition of absolute ethanol gave crystals of 2-(3-diethylamino-1-amino-*n*-propyl) *p*-nitrobenzoate dihydrochloride (V), 0.645 g. (97% crude), m.p. 185–190° (gas). Purified as described above, it melted at 194–195° (gas).

This compound (V) was dissolved in sodium bicarbonate solution, allowed to stand ten minutes, then acidified to give N-(3-diethylamino-2-hydroxy-*n*-propyl)-*p*-nitrobenzamide hydrochloride (I) in 76% yield.

Acknowledgment. The help of Mr. W. C. Alford, Mrs. M. O. Ledyard, and Mrs. E. G. Peake of the microanalytical laboratory is gratefully acknowledged.

SUMMARY

The formation of oxazolines by the action of thionyl chloride on β-hydroxyalkylamides appears to go by way of the chlorosulfinate. Erroneous interpretations in this series are believed due to the similarity in behavior of oxazoline salts and β-haloalkylamides.

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POTENTIAL ANTIMALARIALS. (2-PHENYL-7,8-BENZOQUINOLYL-4)-α-PIPERIDYLCARBINOLS[1]

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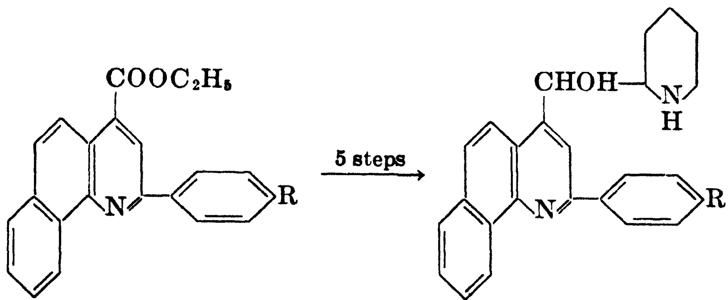
(2-Phenyl-7,8-benzoquinolyl-4)-α-piperidylcarbinols Va and Vb were prepared in the usual manner (1) starting from the corresponding esters Ia and



Series a: R = H
b: R = Cl

Ib which were obtained via the Doebner reaction. The antimalarial activities of Va (SN 10,534) and of Vb (SN 12,895) are tabulated in the Wiselogle Monograph (2).

A preliminary attempt was made to synthesize carbinols in the 5,6-benzoquinolyl-4 series; it was found that, undoubtedly due to the steric effect of the 5-substituent (3), ethyl 2-phenyl-5,6-benzocinchoninate (VI) did not condense smoothly with ethyl benzamidocaproate (II).

Acknowledgment. Mr. J. A. Seneker aided in the preparation of esters I; Dr. H. Sargent and Mr. T. C. Myers carried out the experiments involving VI. Supplies of II were furnished by Dr. E. B. Hartshorn (Dartmouth College), by Dr. R. C. Elderfield (Columbia University), and by Dr. C. C. Price (then University of Illinois). Microanalyses were performed by Dr. G. Oppenheimer and Mr. G. A. Swinehart.

EXPERIMENTAL[3]

BENZOCINCHONINIC ESTERS

Ethyl 2-phenyl-7,8-benzocinchoninate (Ia) (4). The Doebner condensation (4) was carried out in ethanol, heating for four hours; a 50% aqueous pyruvic acid (supplied by the Calco

[1] The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the California Institute of Technology.

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[3] All melting points are corrected.

Chemical Division of the American Cyanamid Company) was used. The crude acid, after washing with ethanol, was esterified with ethanolic sulfuric acid. The reaction mixture was poured into ice-water and basified; the ester was extracted with benzene and recrystallized from ethanol, m.p. 96° [lit. (4) m.p. 103°], yield 18.6% from α-naphthylamine.

Ethyl 2-(p-chlorophenyl)-7,8-benzocinchoninate (Ib). A mixture of 572.8 g. (4 moles) of α-naphthylamine, 562.4 g. (4 moles) of p-chlorobenzaldehyde, 704 g. (*ca.* 4 moles) of 50% aqueous pyruvic acid, and 10 l. of 95% ethanol was refluxed for *ca.* sixteen hours. The crude product was washed with 95% ethanol and dried, yield 705 g.; a portion, on recrystallization from glacial acetic acid, gave yellow microneedles, m.p. 308–309°.

Anal. Calc'd for $C_{20}H_{12}ClNO_2$: N, 4.20. Found: N, 4.19.

This acid was refluxed for forty-one hours with 9 l. of ethanol and 400 ml. of concentrated sulfuric acid and the solution evaporated *in vacuo* to *ca.* 2 l. The residual sirup was poured on ice and the ester extracted with benzene. The extracts were washed with 1 *N* sodium hydroxide and evaporated to a thick oil which was taken up in 600 ml. of ethanol. On cooling, crude tarry ester separated (470 g.) which was recrystallized from a mixture of 940 ml. of ethanol and 610 ml. of benzene; yield (after washing with ethanol) 167.3 g. (11.5% from α-naphthylamine), m.p. 124–126°. A portion was recrystallized from ethanol-benzene, dense tufts of tan bars m.p. 127.4–127.8°.

Anal. Calc'd for $C_{22}H_{16}ClNO_2$: C, 73.03; H, 4.46; N, 3.87.

Found: C, 72.86; H, 4.76; N, 3.89.

Ethyl 2-phenyl-5,6-benzocinchoninate (VI). β-Naphthylamine (280 g., 1.95 moles) was condensed (4) in ethanol with benzaldehyde and 50% pyruvic acid (one hour) and the mixture was cooled to *ca.* 60° and filtered. The crude acid was washed with ethanol and dried, yield 268.5 g. Since esterification with ethanolic sulfuric acid proceeded too slowly to be feasible, 261.6 g. of this acid was converted to the acid chloride (heating on steam-bath for three and one-half hours with 330 ml. of purified thionyl chloride; removing excess of latter on steam-bath *in vacuo*) and this was refluxed for two hours with 500 ml. of ethanol. After diluting the mixture with water and making basic with 15 *N* ammonium hydroxide, the ester was extracted with ether and recrystallized from ethanol, yield 205.7 g. (m.p. 82–83°) plus 22.5 g. from the mother liquors (36.5% from β-naphthylamine). A portion of VI was recrystallized from ethanol, pearly flakes, m.p. 83.5–84.0°.

Anal. Calc'd for $C_{22}H_{17}NO_2$: C, 80.71; H, 5.24; N, 4.28.

Found: C, 80.58; H, 5.12; N, 4.43.

Simon and Mauguin (5) claim to have prepared VI by the action of ethyl pyruvate on benzal-β-naphthylamine but report no characterization. VI boils at *ca.* 200° at 2 mm. and gives a *picrate*, m.p. 192.0–192.5°.

Anal. Calc'd for $C_{28}H_{20}N_4O_9$: C, 60.43; H, 3.62; N, 10.07.

Found: C, 60.39; H, 3.65; N, 10.13.

The corresponding methyl ester was made from the acid chloride and methanol, needles, m.p. 126.5–126.7° from ethanol-isopropanol [lit. (6) m.p. 125°, 128°].

PIPERIDYLCARBINOLS

Except where otherwise noted, the general procedures were those employed in a previous publication (1d).

ε-(2-Phenyl-7,8-benzocinchoninyl)-n-amylamine hydrobromide (IIIa). A solution of 201 g. (0.615 mole) of Ia and 161 g. of II in 370 ml. of benzene was heated with sodamide (from 17.7 g. of sodium) for twenty-eight hours. After hydrolysis by refluxing for thirty-seven hours with a solution of 319 ml. of sulfuric acid in 457 ml. of water, the reaction mixture was made basic and extracted with chloroform. The extracts were freed of solvent (steam-bath, *in vacuo*) and the residue (160.5 g.) treated with 71 g. of 48% hydrobromic acid and *ca.* 250 ml. of isopropanol. When crystallization was complete, the product (crude IIIa) was filtered off, washed with isopropanol, and air-dried; yield 119.2 g., m.p. 218–221°. From a portion, the free base (compare 1c) was liberated and taken up in benzene; after removal of solvent it was obtained crystalline by moistening with ligroin and scratching, m.p. 69–72°. Another portion of the salt was recrystallized from ethanol—48% hydrobromic

acid, clusters of tiny, bright yellow needles (possibly dihydrobromide), m.p. 225–226° dec. (slow heating; on rapid heating m.p. 237° sl. dec.). An analytical sample was prepared by recrystallizing crude IIIa from glacial acetic acid, clusters of yellow-brown needles, m.p. 206–207°.

Anal. Calc'd for $C_{25}H_{24}N_2O{\cdot}HBr$: C, 66.81; H, 5.61; N, 6.24.

Found: C, 66.64; H, 5.77; N, 6.19.

ε-Bromo-ε-(2-phenyl-7,8-benzocinchoninyl)-n-amylamine hydrobromide[4] (*IVa*). Crude IIIa (94.3 g.) was dissolved in 105 ml. of 48% hydrobromic acid at 60° and treated rapidly with a solution of 33.6 g. of bromine in 27 ml. of the same solvent. An oil precipitated which rapidly dissolved on heating; on subsequent cooling a crystalline cake was obtained. To the mixture was added 275 ml. of 48% hydrobromic acid, 520 ml. of isopropanol, 815 ml. of ethanol, and 320 ml. of water and the cake was dissolved by heating to boiling. After cooling overnight, the resulting mass of orange–yellow needles was filtered off, washed with ethanol, and air-dried; yield 99.6 g. (36.3% from Ia), m.p. 196° dec.; a sample was analyzed directly.

Anal. Calc'd for $C_{25}H_{23}BrN_2O{\cdot}HBr{\cdot}2H_2O$: C, 53.21; H, 5.00; N, 4.97.

Found: C, 53.50; H, 4.84; N, 4.93.

IVa dihydrate was recrystallized from glacial acetic acid, orange-yellow clusters, m.p. 191.8–192.2° (sample inserted in m.p. bath at 170°).

Anal. Calc'd for $C_{25}H_{23}BrN_2O{\cdot}HBr$: C, 56.83; H, 4.58; N, 5.30.

Found: C, 56.75; H, 4.63; N, 5.11.

(2-Phenyl-7,8-benzoquinolyl-4)-α-piperidylcarbinol (*Va*). A mixture of 60.9 g. (0.108 mole) of IVa dihydrate, 1500 ml. of ethanol, and 232 ml. of 14% aqueous sodium carbonate was shaken for eighty minutes. After reduction (0.75 g. of catalyst, twenty-five hours, 3.05 l. of hydrogen) the suspension was heated together with 300 ml. of butanone and 450 ml. of benzene and inorganic solids were filtered off and washed with hot benzene and ethanol. The filtrates were evaporated on the steam-bath, the residue was treated with water-chloroform and undissolved organic solids were combined with the chloroform phase. The chloroform suspension was freed of solvent (finally by boiling off small portions of 95% ethanol from the residue), 100 ml. of 95% ethanol was added, and the mixture was saturated with dry hydrogen chloride; the precipitate was filtered off, washed with isopropanol, and air-dried, yield 50.7 g., m.p. 266°. This product was recrystallized from 100 ml. of water plus 190 ml. of 12 *N* hydrochloric acid using Norit, large clusters of well-formed needles, m.p. 258° dec., yield 50.6 g. (quantitative from IVa; 36.3% over-all from Ia, 63.1% taking into account recovered cinchoninic acid).

Anal. Calc'd for $C_{25}H_{24}N_2O{\cdot}2HCl{\cdot}1.5H_2O$: C, 64.10; H, 6.24; N, 5.98.

Found: C, 64.16; H, 6.26; N, 5.81.

Va was liberated from the salt by suspending the latter in pyridine-benzene and boiling with 4 *N* sodium hydroxide; the base was taken up in benzene-pyridine and, after evaporation of solvent, was recrystallized from pyridine, compact clusters of tiny needles, m.p. 226.8–227.5°.

Anal. Calc'd for $C_{25}H_{24}N_2O$: C, 81.49; H, 6.57; N, 7.60.

Found: C, 81.23; H, 6.38; N, 7.88.

ε-(2-(p-Chlorophenyl)-7,8-benzocinchoninyl)-n-amylamine hydrobromide (*IIIb*). Ib (173g., 0.478 mole) was condensed with II (twenty-four hours) and the product hydrolyzed (forty-two hours). The hydrolyzate was basified in the presence of benzene, the mixture was filtered using Celite, and the filter cake was washed with hot benzene. After removal of solvent (steam-bath, *in vacuo*) from the combined benzene extracts, the residue (134.7 g.) was treated with 260 ml. of isopropanol, 50 ml. of acetone, and 90.3 g. of 48% hydrobromic acid. The solution obtained on warming was allowed to cool and the resulting mass of fine

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[4] Published studies (7) have made it seem possible to generalize regarding the salt-forming properties of 8-substituted 2-phenylquinoline derivatives. However, in the present work, it was found that IVb (but not IVa) was isolated as a dihydrobromide while Va (but not Vb) formed a stable dihydrochloride.

needle-clusters filtered and washed with isopropanol and with acetone; yield of bright yellow first crop (IIIb) 42.0 g., m.p. 264–265°. The mother liquors plus some ethanol were evaporated to *ca.* 150 ml. and diluted with an equal volume of benzene to give a second crop, 34.7 g., m.p. 245–247°; in the same way a third crop of 27.7 g. was obtained. From samples of these crude salts, the free base (compare Series a) corresponding to IIIb was prepared, m.p. 134–136° after scratching with isopropanol-ligroin; it crystallized slowly even when seeded. A portion of first-crop material was recrystallized from aqueous acetic acid, tan flakes, m.p. 190–191° (m.p. bath heated slowly from 184°; m.p. varies with rate and extent of heating); the analysis indicates *IIIb monohydrate* as a possible formula.

Anal. Calc'd for $C_{25}H_{21}ClN_2O{\cdot}HBr{\cdot}H_2O$: C, 59.83; H, 5.22; N, 5.58.

Found: C, 60.44; H, 5.54; N, 5.78.

Experiments with recrystallized and unrecrystallized material showed that it was advantageous to brominate crude first-crop and second-crop IIIb directly. Third-crop IIIb (22.0 g.) was purified by conversion to the free base which was taken up in benzene and the solution freed of solvent [solids difficultly soluble in benzene (m.p. 194–197°) were discarded]; crude yield 11.8 g.

ε-Bromo-ε-(2-(p-chlorophenyl)-7,8-benzocinchoninyl)-n-amylamine hydrobromide (IVb). Second-crop IIIb (29.1 g.) was suspended in 120 ml. of nearly boiling 48% hydrobromic acid and treated slowly with 9.6 g. of bromine in 12 ml. of the same solvent. The latter was added in portions with heating after each addition until the initially precipitated oil had dissolved. The solution was slowly diluted with 150 ml. of isopropanol and filtered hot (using Celite). The filtrate, on cooling, deposited a bright yellow solid which was filtered off and washed with isopropanol-ether, yield 25.4 g. A portion was recrystallized from glacial acetic acid, tiny, rough, bright yellow bobbins, m.p. 189° dec.

Anal. Calc'd for $C_{25}H_{22}BrClN_2O{\cdot}2HBr{\cdot}H_2O$: C, 45.38; H, 3.96; N, 4.23.

Found: C, 45.63; H, 4.07; N, 4.19.

First-crop IIIb (4.84 g.) gave on bromination 5.78 g. of crude IVb, m.p. 170°. The crude base (11.8 g.) from third-crop IIIb gave 15.0 g. of crude IVb.

(2-(p-Chlorophenyl)-7,8-benzoquinolyl-4)-α-piperidylcarbinol (Vb). Crude IVb (14.6 g.) from third-crop IIIb, 400 ml. of ethanol, and 58 ml. of 14% aqueous sodium carbonate were shaken for eighty minutes and reduced (3.0 g. of catalyst, eleven hours, 1.47 l. of hydrogen). The mixture, after the addition of 160 ml. of benzene, was heated to boiling and filtered and the filter cake was extracted with 50 ml. of boiling benzene. The combined solutions were freed of solvent and the crystalline residue washed well with water and dried. The product (8.8 g.) was taken up in 25 ml. of boiling pyridine and the solution was diluted with 50 ml. of hot benzene and allowed to crystallize. Yield, 6.0 g. of fine white needle-clusters, m.p. 224.9–225.5° (sintering from 223°).

Anal. Calc'd for $C_{25}H_{23}ClN_2O$: C, 74.52; H, 5.75; N, 6.95.

Found: C, 74.93; H, 6.01; N, 6.66.

Crude IVb (4.77 g.) from first-crop IIIb gave on reduction 1.93 g. of recrystallized Vb; 25.4 g. of IVb from second-crop IIIb gave 7.2 g. of recrystallized carbinol. These figures indicate an 18.2% over-all yield from Ib. A solution of 17.8 g. of Vb in 103 ml. of glacial acetic acid and 80 ml. of 12 *N* hydrochloric acid was diluted with 700 ml. of methanol and then, with swirling, 27 ml. of water was added. The finely-divided solid which separated was filtered off, washed with aqueous methanol, and dried; yield 17.2 g., m.p. 256–258° (slow heating from 242°).

Anal. Calc'd for $C_{25}H_{23}ClN_2O{\cdot}HCl{\cdot}0.5H_2O$: C, 66.96; H, 5.62; N, 6.25.

Found: C, 66.57; H, 5.69; N, 6.13.

SUMMARY

(2-Phenyl-7,8-benzoquinolyl-4)-α-piperidylcarbinol and [2-(p-chlorophenyl)-7,8-benzoquinolyl-4]-α-piperidylcarbinol have been prepared.

PASADENA 4, CALIF.

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[Contribution from the Bureau of Agricultural and Industrial Chemistry, and the Bureau of Plant Industry, Soils, and Agricultural Engineering, Agricultural Research Center

SYNTHETIC PLANT-GROWTH REGULATORS

I. 2,4-Dichloro-5-iodophenoxyacetic Acid and Derivatives

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The application of plant-growth regulators to specific agricultural problems has created considerable interest in this field of research. Many compounds have been tested and some have been found active, but their mechanism of action is not understood. Our earlier work (1, 2) on the translocation of a radioactive labeled plant-growth regulator, 2-iodo^{131}-3-nitrobenzoic acid, gave very promising results. However since certain of the phenoxyacetic acids are the most powerful regulators discovered to date, an investigation of the mechanism of action of a typical phenoxyacetic acid would contribute much to our knowledge. The synthesis and properties of new plant-growth regulators, 2,4-dichloro-5-iodophenoxyacetic acid and 15 of its derivatives, are the subject of this paper. The synthesis of 2,4-dichloro-5-iodophenoxyacetic acid and its derivatives containing radioactive iodine, used in translocation and mechanism of action investigations, is the subject of Part II of this paper.

EXPERIMENTAL

2,4-Dichloro-5-nitrophenoxyacetic acid. The synthesis of this compound was conducted, in part, in accordance with the instructions of Newman and Wotiz (3). Twenty-two g. of *finely* ground 2,4-dichlorophenoxyacetic acid (4), recrystallized from benzene, and of m.p. 140–141°, was added, with shaking, to 80 ml. of C.P. fuming nitric acid (*sp. gr.* 1.50) and allowed to react for 1½ to 2 minutes at 30–40°. To stop the reaction the clear, orange solution was poured on to 400 g. of crushed ice. The crude product was recrystallized first from 50% ethanol, m.p. 155–157° (yield 70%), and finally from a mixture of 85% benzene and 15% absolute ethanol to yield 2,4-dichloro-5-nitrophenoxyacetic acid, m.p. 158.5–159.5° (cor.) (yield 50%).

Anal. Calc'd for $C_8H_5Cl_2NO_5$: C, 36.16; H, 1.88; Cl, 26.65; N, 5.93; Neut. equiv., 266.0.
Found: C, 36.24; H, 1.99; Cl, 26.61; N, 5.90; Neut. equiv., 265.5.

5-Amino-2,4-dichlorophenoxyacetic acid. This product, m.p. 173.5–174.5° (cor.), was prepared in 95% yield by the reduction of 100 g. of 2,4-dichloro-5-nitrophenoxyacetic acid with ferrous sulfate and ammonia by the method of Jacobs and Heidelberger (5).

Anal. Calc'd for $C_8H_7Cl_2NO_3$: C, 40.70; H, 2.99; Cl, 30.04, N, 5.26.
Found: C, 41.1; H, 3.1; Cl, 29.9; N, 5.25.

2,4-Dichloro-5-iodophenoxyacetic acid. The sodium salt of 5-amino-2,4-dichlorophenoxyacetic acid (11.81 g.) was diazotized in sulfuric acid at 0–5°. Urea was added to destroy excess nitrous acid. Twenty ml. (8.72 g.) of potassium iodide was then added rapidly, with stirring, and the reaction mixture warmed to 70–80° for thirty minutes, then cooled, filtered with suction and the product washed with 5% sodium bisulfite and water. The product, recrystallized from 50% ethanol, was obtained in a 65% yield, m.p. 151.5–152.5° (cor.).

Anal. Calc'd for $C_8H_5Cl_2IO_3$: C, 27.69; H, 1.45; I, 36.58.
Found: C, 27.71; H, 1.72; I, 36.83 (assuming theor. % Cl).

5-Acetamino-2,4-dichlorophenoxyacetic acid. This product was prepared from 5-acetamino-2,4-dichlorophenol by the method of Synerholm and Zimmerman (5). The crude

product, m.p. 199–209°, when recrystallized from 95% ethanol melted at 213.5–214.5°, cor., (yield 49%). The structure of 5-amino-2,4-dichlorophenoxyacetic acid was established by acetylation to the 5-acetamino derivative. The product melted at 213.5–214.5° (cor.) and the melting point was not depressed by mixing with a sample of the compound prepared from 5-acetamino-2,4-dichlorophenol.

Anal. Calc'd for $C_{10}H_9Cl_2NO_4$: C, 43.19; H, 3.27; Cl, 25.49; N, 5.03.
Found: C, 43.18; H, 3.23; Cl, 25.60; N, 4.97.

PREPARATION AND PLANT-GROWTH REGULATING ACTIVITY OF DERIVATIVES OF 2,4-DICHLORO-5-IODOPHENOXYACETIC ACID

The derivatives of 2,4-dichloro-5-iodophenoxyacetic acid prepared by chemists of the Bureau of Agricultural and Industrial Chemistry, and tested for plant-growth regulating activity by Mitchell and Linder, Bureau of Plant Industry, Soils, and Agricultural Engineering, are listed in Table I. The inhibition of growth in the terminal bud of test kidney bean seedlings was used to compare the regulating activity of 2,4-dichloro-5-iodophenoxyacetic acid and its derivatives with the activity of 2,4-dichlorophenoxyacetic acid. The activity of 2,4-dichloro-5-iodophenoxyacetic acid was found to be only about 60% that of 2,4-dichlorophenoxyacetic acid, showing the marked influence of iodine in the 5-position. On the other hand, the esters and amide were found to have a greater activity than their parent acid, 2,4-dichloro-5-iodophenoxyacetic acid, when tested on an equivalent weight basis, whereas, the salts had lower or no better activity than their parent acid. The activity of some esters approached, but in no case reached, the activity of 2,4-dichlorophenoxyacetic acid. Detailed results of the plant-growth regulating activity of 2,4-dichloro-5-iodophenoxyacetic acid and its derivatives will be reported elsewhere.

II. RADIOACTIVE LABELED 2,4-DICHLORO-5-IODO^{131}-PHENOXYACETIC ACID AND DERIVATIVES

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In Part I of this paper the synthesis of stable 2,4-dichloro-5-iodophenoxyacetic acid (2,4-D-5-I) has been reported. Part II will describe the apparatus used in the synthesis of 2,4-D-5-I and its derivatives containing radioiodine, the distribution of radioiodine in product and by-products during the synthesis, and the use of this compound for investigating the mechanism of action of plant-growth regulators.

EXPERIMENTAL

2,4-Dichloro-5-iodo^{131}-phenoxyacetic acid. The reaction apparatus shown in Figure 1 was mounted on a stainless steel pan behind an L-shaped lead shield, 2 inches thick with a front vertical section 20 inches wide and 24 inches high, and in a well-ventilated hood. A control panel was mounted on the front vertical section of the lead shield. Other shielding was provided by portable lead bricks, 2 × 4 × 8 inches in size. Manipulative work was conducted with extension tongs.

Diazotization of 5-amino-2,4-dichlorophenoxyacetic acid (11 81 g.) and reaction with

potassium iodide containing 20 mc.I^{131} were conducted in beaker A by procedures given in Part I of this paper. The crude product was cooled to 15–20° and then transferred with vacuum to funnel B, the filtrate being allowed to run into flask C and then into flask D. The crude product was washed with 5% sodium bisulfite solution, then with water, and the

TABLE I

DERIVATIVES OF 2,4-DICHLORO-5-IODOPHENOXYACETIC ACID

DERIVATIVES	M.P., °C (COR.)	EMPIRICAL FORMULA	ANALYSIS		
			Element	Calc'd, %	Found, %
Ammonium salt[a]	234–235	$C_8H_8Cl_2INO_3$	Nitrogen	3.85	3.71
Ethylammonium salt[a]	194–195	$C_{10}H_{12}Cl_2INO_3$	Nitrogen	3.57	3.56
Diethylammonium salt[b]	145.5–146.5	$C_{12}H_{16}Cl_2INO_3$	Nitrogen	3.33	3.32
Morpholine salt[b]	193.5–197.5	$C_{12}H_{14}Cl_2INO_4$	Nitrogen	3.20	3.22
Triethanolamine salt[a]	113–114	$C_{14}H_{20}Cl_2INO_6$	Nitrogen	2.82	2.97
Sodium salt[c]		$C_8H_4Cl_2INaO_3$	Sodium	6.23	6.22
Potassium salt[c]		$C_8H_4Cl_2IKO_3$	Potassium	10.15	9.94
Calcium salt[d]		$C_{16}H_8CaCl_4I_2O_6$	Calcium	5.48	5.38
Cupric salt[d]		$C_{16}H_8Cl_4CuI_2O_6$	Copper	8.41	8.41
Acid chloride[e]		$C_8H_4Cl_3IO_2$	—	—	—
Methyl ester[f]	109.5–111.5	$C_9H_7Cl_2IO_3$	Carbon	29.94	30.02
			Hydrogen	1.95	2.10
			Iodine	35.16	35.01
Ethyl ester[f]	83.5–84.5	$C_{10}H_9Cl_2IO_3$	Iodine	33.84	33.82
Isopropyl ester[f]	88–89	$C_{11}H_{11}Cl_2IO_3$	Carbon	33.87	34.04
			Hydrogen	3.10	3.14
n-Butyl ester[f]	70.5–71.0	$C_{12}H_{13}Cl_2IO_3$	Carbon	35.75	35.77
			Hydrogen	3.25	3.48
Amide[g]	160–161	$C_8H_6Cl_2INO_2$	Nitrogen	4.05	4.05

[a] An ethanol solution of dry ammonia or amine was added to an ethanol solution of the acid. The ethylammonium and triethanolamine salts were then recrystallized from ethanol.

[b] The acid was reacted with excess amine at room temperature and the reaction mixture diluted with ethanol. The diethylammonium salt was recrystallized from benzene and the morpholine salt from ethanol.

[c] The calculated amount of one-normal alkali solution was added to an ethanol solution of the acid. The salt was then recrystallized from 50% ethanol.

[d] An aqueous ethanol solution of metal acetate was added to an ethanol solution of the acid. The calcium salt was recrystallized from 50% ethanol.

[e] The acid was refluxed 1½ hours with excess thionyl chloride; the product was vacuum distilled, boiling at 180°/5 mm.

[f] The acid chloride was refluxed 1½ hours with excess absolute alcohol and the ester was recrystallized from 50% ethanol.

[g] The acid chloride was treated with ice cold conc'd ammonia and the amide recrystallized from 50% ethanol.

combined filtrates collected in flask D. Absolute ethanol (150 ml.) was added through E to flask C and the crude 2,4-D-5-I was dissolved by refluxing with hot ethanol. The hot ethanolic solution of 2,4-D-5-I was drawn from funnel B into flask C by applying vacuum at point *1*, and then forced from flask C, with a slight pressure applied at point *1*, into a 500-ml. round-bottomed flask (position—beaker A) and heated with 0.5 g. of activated carbon.

The hot solution was transferred to funnel B, filtered to remove the carbon, and the filtrate collected in flask C. Pressure was then applied at point *1*, and the hot filtrate was forced out of flask C into flask G. Hot water (150 ml.) was then added to flask G and the contents thoroughly mixed, then cooled and filtered. Ten g. of nonradioactive 2,4-dichloro-5-iodophenoxyacetic acid, as carrier, was added to the moist radioactive product. The final product, recrystallized from 50% ethanol, melted at 151.5–152.5° (yield 18.1 g.).

If it is assumed that a complete recovery of the nonradioactive acid (10.0 g.) was achieved, then 8.1 g. of radioactive material or 47% of theory was obtained on the basis of the radioactive synthesis. The specific activity of the acid (18.1 g.) was 5.79 (±) 0.06 × 10^3 counts per second per milligram, which accounted for approximately 47% of the radioactivity intro-

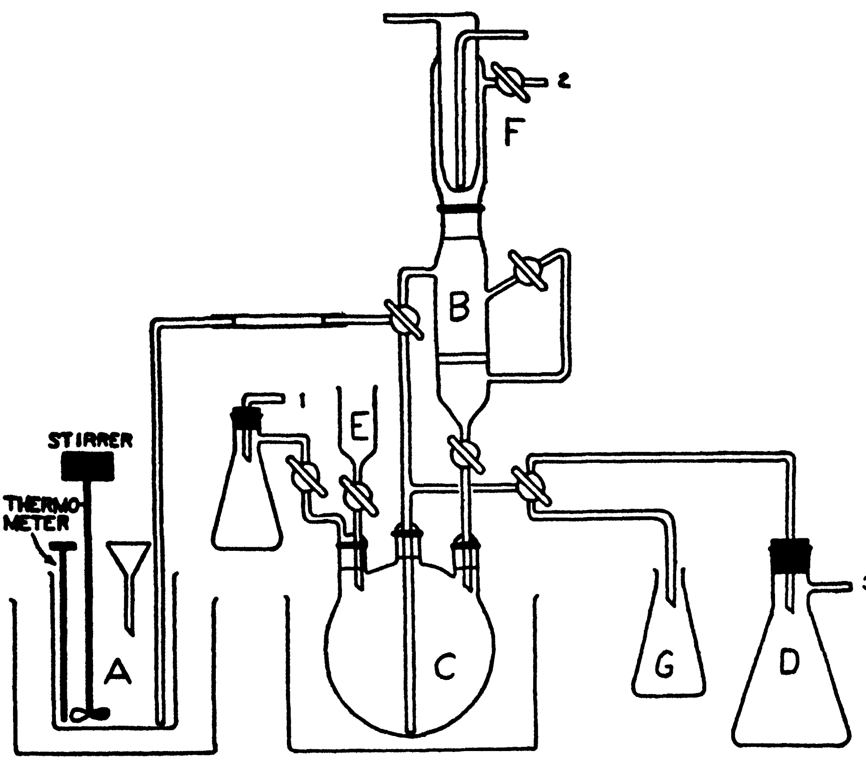

FIGURE 1. REACTION APPARATUS

duced in the synthesis. The distribution of radioactivity in this synthesis is given in Table II.

Derivatives of 2,4-dichloro-5-iodo^{131}-phenoxyacetic acid. The following eleven derivatives were prepared, essentially as stated in Part I of this paper: ammonium, ethylammonium, diethylammonium, triethanolamine, sodium, and calcium salts; acid chloride; amide; and methyl, isopropyl, and *n*-butyl esters.

RADIOACTIVITY MEASUREMENTS

Radioactivity assays were made on aliquots of the original radioiodide^{131} solution,[1] an alcoholic solution of recrystallized 2,4-dichloro-5-iodo^{131}-phenoxyacetic acid, the re-

[1] Radioiodine was obtained through the Isotopes Branch, Manhattan District, Oak Ridge, Tennessee.

TABLE II

DISTRIBUTION OF RADIOACTIVITY IN SYNTHESIS OF 2,4-DICHLORO-5-IODO^{131}-PHENOXYACETIC ACID

MATERIAL	DILUTION RATIO OF ASSAY SOLUTION	COUNTING RATE[a] OF ASSAY SOLUTION COUNTS/SEC./0.1 ML.	SPECIFIC ACTIVITY OF MATERIAL COUNTS/SEC./ML.	AMOUNT OF MATERIAL	TOTAL RADIOACTIVITY PRESENT IN MATERIAL		TOTAL RADIOACTIVITY ACCOUNTED FOR PER CENT
					Counts/sec.	Millicuries[b]	
Radioiodide^{131} used in synthesis..	1:25,000	37.5 ± 0.4	$9.38 \pm 0.10 \times 10^{6}$	24 ml.	$2.25 \pm 0.03 \times 10^{8}$	20.1 ± 0.7	100.0
Recrystallized 2,4-Dichloro-5-iodo^{131} phenoxyacetic acid....	—	29.8 ± 0.33[c]	$5.79 \pm 0.06 \times 10^{3}$[d]	18.1 g.	$1.05 \pm 0.01 \times 10^{8}$	9.5 ± 0.3	47.3
Reaction mixture + washings.	1:25	100.5 ± 1.11	$2.51 \pm 0.03 \times 10^{4}$	1120 ml.	$2.81 \pm 0.03 \times 10^{7}$	2.5 ± 0.1	12.4
Mother liquor from 1st recrystallization..	1:58.8	122.0 ± 1.34	$4.88 \pm 0.05 \times 10^{4}$	340 ml.	$2.44 \pm 0.03 \times 10^{7}$	2.2 ± 0.1	10.9
Mother liquor from 2nd recrystallization......	1:10	330.0 ± 3.63	$3.30 \pm 0.04 \times 10^{4}$	485 ml.	$1.60 \pm 0.02 \times 10^{7}$	1.4 ± 0.1	7.0
Radioactivity unaccounted for (possibly present in carbon black and in residues on walls of reaction vessels and filtration apparatus)....							22.4
Total.........							100.0

[a] All values are at zero absorber and have been corrected for decay, coincidence, etc.

[b] Total disintegration rate,

$$\text{millicuries (mc.)} = \frac{\text{total radioactivity (counts/sec.)} \times \text{geometry (3.34 disintegrations/count)}}{3.7 \times 10^{7}}$$

[c] 0.1 ml. = 0.00515 mg. acid

[d] counts/sec./mg.

action mixture plus washings, and the mother liquors from the first and second recrystallizations of the acid. The aliquots were diluted with a special dilution medium[2] composed of 0.02 *M* sodium hydroxide, 0.0015 *M* potassium iodide, and 0.005 *M* sodium bisulfite.

Samples were prepared, for counting, by transferring 0.1-ml. aliquots of the various solutions by means of calibrated micro-pipettes to the surfaces of palladium-faced silver disks,[3] $\frac{1}{16}$ inch thick by 1 inch in diameter. One drop of a dilute aqueous silver nitrate solution (1 mg./ml.) was then added to the deposit, and the latter was evaporated to dryness under an infra-red heat lamp. Measurements were carried out by means of a Victoreen counter, Model VG-10[4] with mica window 2.6 mg./cm^2, and an Autoscaler[5] having a scaling ratio of 4096.

The counting rates of the samples were determined by measuring the samples with calibrated aluminum absorbers of various thicknesses interposed before the window of the counter. The counting rates, after being corrected for background (13-14 counts/minute with the counter in a lead shield having a wall thickness of two inches) and decay, were plotted on triple cycle semi-logarithmic graph paper as a function of activity (ordinate) versus absorber thickness (abscissa), taking into account the thickness of the counter window and the absorption of the beta particles in the air above the sample. The specific activities at zero absorber were then obtained by extrapolation. The values had an overall accuracy of (±) 1.1% (probable error). The absolute disintegration rates of the various radioiodine samples were then calculated from the values for the specific activities at zero absorber and the geometry and efficiency of the counter. The latter value was found to be 3.34 disintegrations per count as determined from the ratio of the absolute disintegrations rate of a calibrated Radium D + E standard[6] to its counting rate at zero absorber, obtained in the same manner as that of the radioiodine solutions.

TRACER EXPERIMENTS

These compounds were applied to a considerable number of different plants, and they were found to accumulate primarily in the young meristematic tissues. For prolonged investigations compounds of higher specific activity are required and they can be synthesized using the procedures and apparatus described. The detailed results on the translocation and mechanism-of-action investigations on plants will be published elsewhere.

Acknowledgments. The authors are indebted to Mr. J. S. Ard of this Laboratory, and to Drs. C. O. Willits and C. L. Ogg, Eastern Regional Research Laboratory, for the analyses reported in this paper.

SUMMARY

A new synthetic plant-growth regulator, 2,4-dichloro-5-iodophenoxyacetic acid and 15 of its derivatives have been synthesized and their biological prop-

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[2] Recommended by the Monsanto Chemical Company, formerly of the Clinton Laboratories, Oak Ridge, Tennessee, and the Radioactivity Section of the National Bureau of Standards, Washington, D. C.

[3] Obtained through the courtesy of Dr. L. F. Curtiss, Radioactivity Section, National Bureau of Standards, Washington, D. C.

[4] Victoreen Instrument Company, Cleveland, Ohio.

[5] Tracerlab Inc., Boston, Massachusetts.

[6] This standard, calibrated and furnished by the Radioactivity Section, National Bureau of Standards, Washington, D. C., was found to have an absolute activity of 108.9 (± 2%) disintegrations/sec. on December 29, 1948, after correcting for its decay following the calibration date.

erties studied. The new plant-growth regulator and eleven derivatives containing radioiodine have been synthesized. The apparatus used in these syntheses is described, and the distribution of radioactivity in the synthesis of 2,4-dichloro-5-iodo^{131}-phenoxyacetic acid is recorded. The use of these compounds in investigations on the mechanism of action of phenoxyacetic acid type plant-growth regulators is indicated.

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(4) POKORNY, *J. Am. Chem. Soc.*, **63**, 1768 (1941); SYNERHOLM AND ZIMMERMAN, *Contribs. Boyce Thompson Inst.*, **14**, 95 (1945); EBEL, BELL, FRIES, KASEY, AND BERKEBILE, *J. Chem. Education*, **24**, 449 (1947).
(5) JACOBS AND HEIDELBERGER, *J. Am. Chem. Soc.*, **39**, 1435 (1927).

[Contribution from the Research Laboratories of The Upjohn Company]

PHYSIOLOGICALLY ACTIVE INDANAMINES. III. THE SYNTHESIS OF THE CYCLIC ANALOG OF EPHEDRINE

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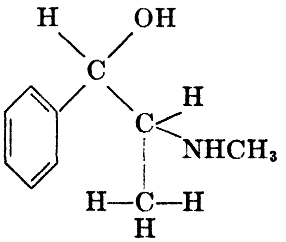
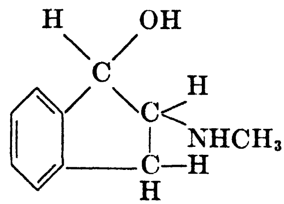
A number of indanamines reported previously from this laboratory (1, 2) have shown promising bronchodilator activity. The present paper describes the synthesis of the cyclic form of ephedrine (I), namely, 2-methylaminoindanol (II). By the Sollmann and von Oettingen perfused lung method this compound has been found to possess somewhat greater bronchodilator activity than ephedrine.[1] The corresponding benzyl ether (IV) appears to be considerably more potent than II.



I.



II.

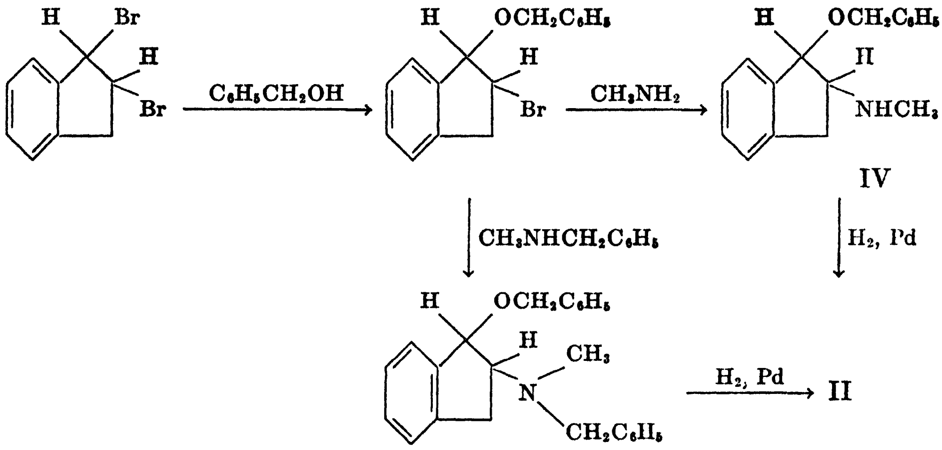
Earlier efforts (1) to prepare 2-methylaminoindanol by the Becker-Decker alkylation of 2-aminoindanol were unsuccessful. von Braun and Weissbach (3) reported isolation of traces of the compound as the picrate by selective demethylation of its methyl ether. In the current studies, attempts to alkylate methylamine and benzylmethylamine with 2-bromoindanone, followed by reduction of the carbonyl group and debenzylation, gave unsatisfactory results.[2] Another approach to the problem was based on a report by Manske and Johnson (4) that 1-phenylpropanedione-1,2 on reductive amination with methylamine gave ephedrine, and by Koelsch and le Claire (5) that the β-keto group of indandione-1,2 was the more reactive. Several attempts at catalytic reductive amination of indandione with methylamine failed to give a characterizable compound. Likewise efforts to reduce this Schiff base with lithium aluminum hydride (6) were unsuccessful, a very dark solution being formed as soon as the amine

[1] Assays were carried out under the direction of B. E. Graham of our Pharmacology Department.

[2] Since this attempt was made, a statement was found in German Patent 598,142 that bromoindanone with ammonia, methylamine, hexamethylenetetramine, potassium phthalimide, and the potassium salt of N-methyltoluenesulfonamide gave only coupling to indanonylbromoindanone. This has been verified, but it is of interest that with substituted bromoindanones, such as 5,6-dimethoxybromoindanone, such colored self-condensation products are not formed on reaction with amines, and the expected secondary or tertiary aminoindanones are produced.

and ketone were mixed. 2-*p*-Toluenesulfonamidoindanol-1 (III) could be methylated under very limited conditions, but subsequent attempts to cleave the tosyl group with metallic sodium and liquid ammonia (7) met with failure.

The synthesis of II was achieved by the method summarized in the accompanying chart:



This approach consisted of the conversion of 1,2-dibromoindane through indenebromohydrin benzyl ether into 1-benzyloxy-2-methylaminoindane (IV), followed by reductive debenzylation. It has been shown (3) that reaction of 1,2-dibromoindane with methanol gives 1-methoxy-2-bromoindane in good yield, but when ethanol is used the yield is much poorer (8). In the present work the corresponding benzyl ether was obtained in about 45% yield, but reaction of this with methylamine under pressure gave at best 20% yields of the N-methyl benzyl ether.[3] Catalytic hydrogenation with palladium removed the benzyl group to give the desired cyclic analog of ephedrine (II).

EXPERIMENTAL

Sulfonamide alkylations. *p*-Toluenesulfonamidoindanol (III) was prepared by the addition of 2.10 g. (0.011 mole) of *p*-toluenesulfonyl chloride in three portions to a solution of 1.85 g. (0.01 mole) of 2-aminoindanol hydrochloride in 25 cc. of pyridine. The solution was heated on the steam-bath for fifteen minutes, cooled, poured into ice and excess concentrated hydrochloric acid, and chilled overnight. The brown gummy product was spread on a porous plate to dry and purified by recrystallization from toluene, then dilute alcohol, giving pure white crystals, m.p. 137–138°.

Anal. Calc'd for $C_{16}H_{17}NO_3S$: C, 63.50; H, 5.65; N, 4.62.

Found: C, 63.60; H, 5.77; N, 4.59.

Alkylation of the sulfonamide (III) was attempted without success using benzyl chloride, benzyl iodide, and methyl iodide. The sodium, potassium or silver salts of III could not be prepared by standard methods employed for sulfonamides (9), since the free sulfonamide reprecipitated in all cases, even from a cooled solution in excess alkali. The sodium salt was prepared by the following method. Two and five tenths grams (0.008 mole) of *p*-toluenesulfonamidoindanol (III) was dissolved in purified dioxane and the solution added dropwise

[3] This is to be expected from the relative unreactivity of 2-bromoindanes (8).

to a hot, well-stirred suspension of 0.19 g. (0.008 mole) of powdered sodium in 75 cc. of dioxane. Usually a purple color formed almost at once, but in a few cases it was very slight. After addition was complete, the solution was heated under reflux an additional hour and allowed to stand at room temperature. After several days there began to form beautiful white rosettes which were removed and redissolved in hot dioxane. After one or two days the rosettes which formed were collected and dried. They left an ash on ignition, and on addition of water the free sulfonamide was liberated (m.p. 139°). The sodium salt could also be prepared using sodamide in liquid ammonia.

Attempted *alkylations* of the *sodium salt* were unsuccessful under the following conditions: (a) addition of methyl iodide to the liquid ammonia solution without isolation of the sodium salt; (b) heating the sodium salt and methyl iodide in a sealed tube at 150° for seven hours, 140° for fifteen hours or 125° for sixty-three hours; (c) heating the sodium salt under reflux with methyl iodide in benzene, toluene or dioxane. The above alkylation was repeated using a ten-fold excess of methyl iodide in dry xylene under reflux for twenty-two hours. The xylene was chilled, the suspended matter removed by filtration and the filtrate concentrated *in vacuo* to a red-brown gum. This was dissolved in excess hot benzene, decolorized with charcoal, and concentrated to a small volume. On standing overnight there crystallized a white product insoluble in hot alkali. Recrystallization from alcohol gave 0.60 g. (from 1.8 g. of sodium salt) of white crystals (III), m.p. 132.5–133.5°.

Anal. Calc'd for $C_{17}H_{19}NO_3S$: C, 64.34; H, 6.03; N, 4.41.

Found: C, 64.17; H, 6.06; N, 4.42.

The material originally filtered from the cold xylene on extraction with hot benzene yielded considerable quantities of elementary iodine.

Indene dibromide (10). Bromination was carried out by adding an equivalent of bromine dropwise to a solution of indene in ether at 0°. The ether was evaporated at low temperature and the indene dibromide distilled *in vacuo*; b.p. 111° (1.2 mm.); yield, 78%; n_D^{25} 1.6282 [reported (8), 1.6290].

1-Benzyloxy-2-bromoindane. Indene dibromide was stirred for three hours under nitrogen on the steam-bath with one equivalent of benzyl alcohol. The theoretical amount of pyridine (8) was added, the mixture poured into water, and the oil separated, dried, and distilled. Yield, 40%; b.p. 155° (0.22 mm.); n_D^{25} 1.5930.

Anal. Calc'd for $C_{16}H_{15}BrO$. C, 63.36; H, 4.95; Br, 26.40.

Found: C, 63.01; H, 4.92; Br, 25.85.

A reaction between sodium benzylate and indene dibromide yielded only low-boiling products, one fraction, b.p. 77–90° (3 mm.), of which corresponded in boiling point to that reported (8) for 2-bromoindene.

Aminations. When 1-benzyloxy-2-bromoindane was shaken for forty hours at room temperature with a 35% solution of methylamine in benzene no reaction occurred. However, when the reaction was carried out in a sealed tube at an elevated temperature the desired product was isolated in yields up to 20%. Variation of time and temperature indicated the optimum conditions to be approximately 115° for about twenty hours. The methylamine hydrobromide was washed out with water, the benzene and excess methylamine removed *in vacuo* and the residue (IV) converted to its hydrochloride, m.p. 173°. Difficulty was encountered in removing the last traces of methylamine hydrochloride from the product, causing it to have a low carbon and high nitrogen content.

Anal. Calc'd for $C_{17}H_{20}ClNO$: C, 70.46; H, 6.90; N, 4.83.

Found: C, 69.85; H, 6.94; N, 5.05.

Preparation of this compound was also attempted by heating 1-benzyloxy-2-bromoindane with benzylmethylamine and sodium carbonate in a nitrogen atmosphere at 150° for four hours, but without success.

2-Methylaminoindanol hydrochloride (II). Reductive debenzylation of the above benzyl ether was carried out in absolute ethanol with 10% palladium-Norit catalyst. Hydrogen uptake was slow and a crystalline product was isolated by filtering and evaporating the resulting solution to dryness. The *hydrochloride* was recrystallized from ethanol-ether; m.p. 162°.

Anal. Calc'd for $C_{10}H_{14}ClNO$: C, 60.15; H, 7.07; N, 7.02.
Found: C, 60.34; H, 7.23; N, 7.00.

The *picrate*, on recrystallization from absolute ethanol, melted at 169–169.5° [reported m.p., 171° (3)].

SUMMARY

Synthesis of 2-methylaminoindanol, a cyclic analog of ephedrine, is described. Preliminary pharmacological tests indicate that the compound, as well as its corresponding benzyl ether, possesses bronchodilator activity.

KALAMAZOO, MICHIGAN

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF MISSOURI]

2,3′,5-TRIHYDROXYDIPHENYL ETHER[1]

HERBERT E. UNGNADE AND HAROLD HEIN

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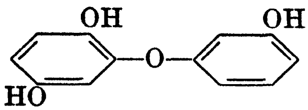
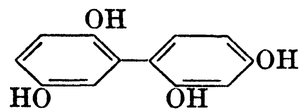
According to Blumenfeld and Friedlander, *p*-benzoquinone and resorcinol react when heated with acid (1) or under the influence of heat alone (2) to give 2,3′,5-trihydroxydiphenyl ether (I). The condensation reaction is supposedly fairly general and applicable to naphthoquinones and various polyhydric phenols.



I



II

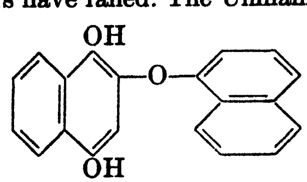
The alternative structure (II) has been proposed for the product of the reaction between benzoquinone and resorcinol by Pummerer and Huppman (3). Both the hydroxydiphenyl and hydroxydiphenyl ether structures, however, appear somewhat doubtful because phenoxy and hydroxyphenyl groups would tend to lower the normal potential of *p*-benzoquinone (4, 5) and thus the formed hydroquinone would be susceptible to oxidation by the original quinone.

Various attempts to repeat the described preparation (1, 2) of (I) have failed to give this substance. It has been possible, however, to isolate hydroquinone in yields of 31% from the reaction mixture, which may be regarded as evidence that the reaction product was at least partially oxidized by the quinone.

In order to obtain further evidence concerning the compounds involved, (I) has been prepared synthetically. 2,3′,5-Trimethoxydiphenyl ether (III) is obtainable through the Ullmann reaction from bromohydroquinone dimethyl ether and the potassium salt of resorcinol monomethyl ether or from *m*-bromoanisole and the potassium salt of hydroxyhydroquinone dimethyl ether. The demethylation of the product with the usual reagents has failed to yield (I). Even hydriodic acid gives only a dihydroxymethoxydiphenyl ether (IV). The complete demethylation of (III) has been effected by the use of aluminum bromide. Since the product and its derivative have physical constants differing from those reported previously (1, 2, 3), the product of Blumenfeld and Friedlander cannot be represented by (I).

Attempts to prepare synthetically another one of the compounds (V) reported by the same authors have failed. The Ullmann reaction of 2-bromo-1,4-

V



[1] From the Master's thesis of Harold Hein.

dimethoxynaphthalene with potassium 1-naphthoxide yields largely 1,4-dimethoxynaphthalene, while the reaction of 1-bromonaphthalene with the potassium salt of 2-hydroxy-1,4-dimethoxynaphthalene yields naphthalene.

EXPERIMENTAL

All temperatures uncorrected. Analyses by Karl Zilch.

Condensation of quinone and resorcinol. Resorcinol (10 g.), mixed with quinone (10 g.) was dissolved in 100 cc. of acetic acid. One cc. of concentrated sulfuric acid was added and the solution was heated at 130° for one hour. The sulfuric acid was neutralized with an equivalent amount of solid sodium bicarbonate. The acetic acid was removed by distillation *in vacuo* and the residue was sublimed from a molecular still in a high vacuum. The sublimate (3.2 g.) melted at 167–169° and did not depress the melting point of a sample of hydroquinone.

Bromohydroquinone dimethyl ether. Hydroquinone dimethyl ether (66 g.) was brominated in 400 cc. of chloroform with 82 g. of bromine dissolved in 30 cc. of chloroform in the presence of 2 g. of iron. The product boiling at 140–144° (16 mm.) weighed 45.2 g.

2,3',5-Trimethoxydiphenyl ether (III). The potassium salt of resorcinol monomethyl ether prepared from 20.8 g. of the phenol was heated with 0.3 g. of copper powder and 44.3 g. of bromohydroquinone dimethyl ether as described previously (6). The steam-distillate of the reaction mixture contained 2.6 g. of hydroquinone dimethyl ether. The non-volatile residue yielded 13.0 g. of trimethoxydiphenyl ether boiling at 160° (1 mm.).

Anal Calc'd for $C_{15}H_{16}O_4$: C, 69.23; H, 6.20.

Found: C, 68.97; H, 6.44.

The substance was also prepared from *m*-bromoaniline and 2-aminohydroquinone dimethyl ether. *m*-Bromoaniline was diazotized and converted to *m*-bromophenol in 60% yield (7). Methylation of this substance with dimethyl sulfate gave 53% of *m*-bromoanisole, b.p. 73–75° (5 mm.). Commercial aminohydroquinone dimethyl ether[2] was diazotized in the usual way. The diazonium sulfate solution was decomposed with sulfuric acid at 130–135° (7), special care being taken to keep the solution ice-cold before it was decomposed. The steam-distillate was extracted with ether. The extract was dried and distilled. 2-Hydroxyhydroquinone dimethyl ether was obtained; b.p. 93–95° (7 mm.). The Ullmann reaction with the potassium salt of this phenol and *m*-bromoanisole gave a 12.6% yield of 2,3',5-trimethoxydiphenyl ether, b.p. 160° (1 mm.).

2,3',5-Dihydroxymethoxydiphenyl ether (IV).[3] Acetic anhydride (10 cc.) and hydriodic acid (2.7 cc., *d.* 1.5) were added to a solution of 1 g. of 2,3',5-trimethoxydiphenyl ether dissolved in 18 cc. of acetic acid. The mixture was refluxed for 1.5 hours and poured into 60 cc. of cold water. The precipitated product (0.5 g.) was crystallized from acetic acid and sublimed at 1×10^{-4} mm. It melted at 150° (dec.).

Anal. Calc'd for $C_{13}H_{12}O_4$: C, 67.24; H, 5.17.

Found: C, 67.80; H, 5.32.

Dibenzoate. Benzoylation of this product (0.15 g.) with benzoyl chloride (0.6 cc.) and 10% aqueous sodium hydroxide gave 0.2 g. of dibenzoate melting at 135–137° (from alcohol).

Anal. Calc'd for $C_{27}H_{20}O_6$: C, 73.64; H, 4.54.

Found: C, 73.67; H, 4.65.

2,3',5-Trihydroxydiphenyl ether. (I). Attempts to demethylate 2,3',5-trimethoxydiphenyl ether with 48% hydrobromic acid and acetic acid or with aluminum chloride in benzene yielded intractable mixtures. Methylmagnesium iodide at 240° effected a demethylation but slightly less than two thirds of the theoretical amount of methane was evolved and the product could not be purified.

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[2] The authors wish to thank the Tennessee Eastman Corporation for a sample of this substance.

[3] It has not been possible to ascertain which methoxyl groups have been cleaved in this compound.

The compound (1 g.) was successfully demethylated by refluxing with aluminum bromide (4.6 g.) and benzene (75 cc.) for four hours. The reaction mixture was decomposed with ice and hydrochloric acid and was extracted with benzene. The product was purified through its sodium salt, regenerated, extracted with ether, dried, and freed from solvent. It solidified on standing and was crystallized from benzene, m.p. 116–118°, yield 0.3 g.

Anal. Calc'd for $C_{12}H_{10}O_4$: C, 66 05; H, 4.59.
Found: C, 65.81; H, 4.85.

Tribenzoate. Benzoylation of the trihydroxy compound (0.1 g.) yielded 0.1 g. of tribenzoate, m.p. 49–51° (from alcohol).

Anal. Calc'd for $C_{33}H_{22}O_7$: C, 74.71; H, 4.15.
Found: C, 74.56; H, 4.24.

2-Bromo-1,4-dimethoxynaphthalene. 1,4-Dimethoxynaphthalene (20 g.) was brominated with 17.0 g. of bromine in chloroform (230 cc.) at room temperature. Iron nails were used as catalyst. The crude bromination product was washed, dried, freed from solvent, and distilled. The distillate boiling at 150° (3 mm.) solidified on cooling. It was crystallized from aqueous alcohol. The colorless crystals melted at 54–55° and weighed 17.2 g.

Anal. Calc'd for $C_{12}H_{11}BrO_2$: C, 53.95; H, 4.43.
Found: C, 53.73; H, 4.54.

1,4-Dimethoxy-2-naphthol. The Grignard reagent from 2-bromo-1,4-dimethoxynaphthalene was oxidized essentially according to Kharasch (8). A solution of 10.7 g of the bromo-compound and 10 g. of isopropyl bromide in 40 cc. of dry ether and 24 cc. of dry benzene was added to 2.9 g. of magnesium, 5 cc. of ether, and a crystal of iodine. After complete addition, the mixture was stirred for thirty minutes. It was oxygenated during twenty minutes, was allowed to stand overnight, and decomposed with aqueous sulfuric acid. The naphthol was removed from the combined ether extracts with 10% aqueous potassium hydroxide containing a small amount of sodium hydrosulfite. The basic solution was acidified with hydrochloric acid, diluted with water (40 cc.), brought to boiling, and allowed to cool. The precipitate was crystallized from Skellysolve B. It melted at 90.5–92 5°, yield 3.1 g.

Anal. Calc'd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.94.
Found: C, 70.70; H, 6.28.

Ullmann reaction. The reaction between potassium 1-naphthoxide (from 3.4 g. of 1-naphthol), 4.2 g. of 2-bromo-1,4-dimethoxynaphthalene, and copper powder at 230° gave 0.4 g. of 1,4-dimethoxynaphthalene (from the steam-distillate). The non-volatile fraction was a tar.

The volatile product from the reaction of 1-bromonaphthalene (0.78 g.) and potassium 1,4-dimethoxy-2-naphthoxide (from 1.53 g. of 1,4-dimethoxy-2-naphthol) proved to be naphthalene (0.1 g.). The non-volatile fraction (0.4 g.) was sublimed at 150° (1 mm.). The viscous oil possibly represents an oxidation product of 1,4-dimethoxy-2-naphthol.

Anal. Calc'd for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49.
Found: C, 66.73; H, 5.53.

SUMMARY

Authentic 2,3′,5-trihydroxydiphenyl ether has been prepared and characterized by a derivative. It is not identical with the product previously assigned this structure.

COLUMBIA, MISSOURI

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[From the Instituto de Fisiología, Facultad de Medicina]

A NEW SYNTHESIS OF DL-HISTIDINE AND DL-N-METHYLHISTIDINE AND SOME REACTIONS OF 4(5)-IMIDAZOLEALDEHYDE

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4(5)-Imidazolealdehyde was first prepared by Pyman (1) by oxidation of 4(5)-hydroxymethylimidazole. Several years later Pyman (2) condensed the aldehyde with hippuric acid and following the classical Erlenmeyer lines realized his second synthesis of histidine. The first one was also due to Pyman (3) who employed malonic ester and 4(5)-chloromethylimidazole.

Several condensation reactions of the aldehyde were described by Pyman (2) and with more detail and extension by Hubball and Pyman (4). Imidazolealdehyde does not react in all respects as a true aldehyde. It gives no Cannizzaro reaction, or Perkin condensation and is inert towards methylmagnesium iodide. It resists air oxidation quite well.

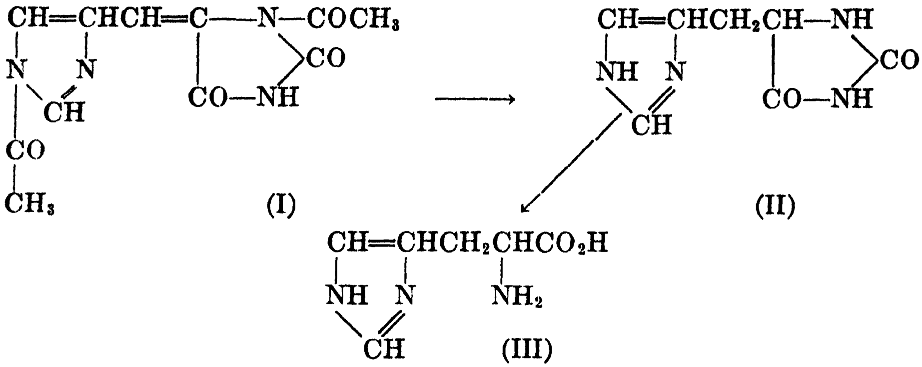
The improvement by Darby, Lewis, and Totter (5) of the primitive method of Girard and Parrod (6) of obtaining hydroxymethylimidazole from fructose, has made imidazolealdehyde accessible in large quantities and allowed the study of a series of condensations from which a new synthesis of DL-histidine and of DL-N-methylhistidine has resulted.

4(5)-Imidazolealdehyde condenses with thiohydantoin, hydantoin, and creatinine by the action of acetic anhydride–sodium acetate. Condensation with acetylthiohydantoin and hydantoin was also obtained with piperidine following the method of Boyd and Robson (7). The 5-imidazolyl-4(5)-methylenethiohydantoin could be desulfurized with monochloroacetic acid and transformed into 5-imidazolyl-4(5)-methylenehydantoin (8).

By condensing imidazolealdehyde with aceturic acid, an unstable azlactone was prepared, that on recrystallization from water yielded the corresponding acrylic acid. The 2,4-dinitrophenylhydrazone was also prepared in the usual way and obtained as the hydrochloride.

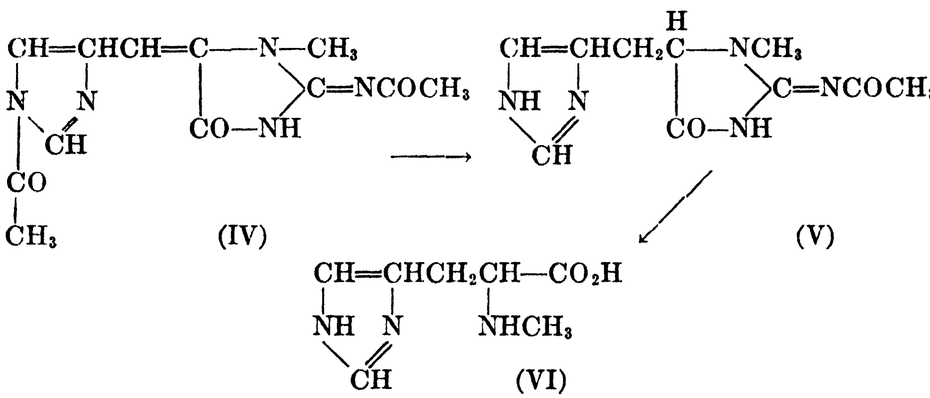
The reduction with sodium amalgam of 5-[1-acetylimidazolyl-4(5)-methylene]-1-acetylhydantoin (I) obtained by condensation of the imidazole aldehyde with hydantoin, yielded 5-[imidazolyl-4(5)-methyl]hydantoin (II) and upon hydrolysis DL-histidine (III) was produced. The racemic 5-[imidazolyl-4(5)-methyl]hydantoin (II) was obtained as a picrate, m.p. 211–212°, with almost the same melting point (209°) as the L isomer, described by Shchukina (9) who prepared it from L-histidine and urea.

This is a new synthesis of histidine (III) and besides the two syntheses of Pyman (2, 3) previously mentioned, two more methods have been described by Albertson and Archer (10) and Albertson and Tullar (11). In both cases they start with 4(5)-chloromethylimidazole and condense it with either ethyl acetamidomalonate or acetamidocyanoacetic ester.



(I) (II) (III)

The application to 5-[1-acetylimidazolyl-4(5)-methylene]-2-acetylcreatinine (IV) of the series of reactions described by Wheeler and Hoffman (12) and Deulofeu and Mendivelzua (13) for the synthesis of N-methylamino acids, gave through the 5-[imidazolyl-4(5)methyl]-2-acetylcreatinine (V), DL-N-methylhistidine (VI).



(IV) (V) (VI)

DL-N-Methylhistidine was synthetized by Fargher and Pyman (14) and many years later by Fishman and White (15) using the same method: condensation of *dl*-α-chloro-β-imidazolylpropionic acid with methylamine. The L isomer was prepared by du Vigneaud and Behrens (16) by methylation of N-*p*-toluenesulfonyl-1-benzyl-L-histidine and subsequent elimination of the *p*-toluenesulfonyl and benzyl groups.

EXPERIMENTAL

The *4(5)-imidazolealdehyde* employed in this work was prepared according to Pyman (2) by oxidation of 4(5)-hydroxymethylimidazole. This compound was obtained by the procedure described by Darby, Lewis, and Totter (5). The stated yields were obtained in both cases.

5-[1-Acetylimidazolyl-4(5)-methylene]-1-acetylthiohydantoin. Imidazolealdehyde (0.2 g.) and thiohydantoin (0.4 g.) were mixed and condensed by the action of 0.4 g. of sodium acetate and 1.6 ml. of acetic anhydride by heating 20 minutes at 135°. Water was added, the precipitate collected, and after drying, recrystallized from an acetic anhydride-acetic acid mixture as dark yellow crystals, m.p. 260–262°.

Anal. Calc'd for $C_{11}H_{10}N_4O_3S$: C, 47.48; H, 3.59; N, 20.14.
Found: C, 47.92; H, 3.85; N, 19.32.

5-[Imidazolyl-4(5)-methylene]thiohydantoin. Imidazolealdehyde (0.15 g.) was mixed with 0.15 g. of acetylthiohydantoin, 0.26 ml. of pyridine, and 0.15 ml. of piperidine and heated at 100° for two minutes. The condensation product separated during the reaction. Water was then added and then acetic acid to maximum precipitation. The solid was recrystallized from ethanol; yellow prisms, m.p. 320°.

Anal. Calc'd for $C_7H_6N_4OS$: C, 43.29; H, 3.09; N, 28.86.
Found: C, 43.82; H, 2.96; N, 27.99.

A sample boiled with acetic anhydride gave a compound of m.p. 257° that was identical with the *diacetyl* derivative already described. Mixed melting point, 257–259°.

5-[1-Acetylimidazolyl-4(5)-methylene]acetylhydantoin. (I). Imidazolealdehyde (2 g.), 4 g. of hydantoin, 4 g. of fused sodium acetate, and 16 ml. of acetic anhydride were heated for 30 minutes at 135° in an oil-bath. The substances dissolved and the condensation product precipitated in crystalline form during the reaction. The mixture was cooled and water added, when more precipitation took place. After 24 hours at 5° the precipitate was recrystallized from a mixture of acetic anhydride-acetic acid; dark yellow crystals, m.p. 246°, almost insoluble in acetic anhydride and water, very soluble in acetic acid; yield 2.9 g. (52 %).

Anal. Calc'd for $C_{11}H_{10}N_4O_4$: C, 50.39; H, 3.81; N, 21.37; CH_3CO-, 32.84.
Found: C, 50.42; H, 4.02; N, 20.81; CH_3CO-, 31.82.

5-Imidazolyl-4(5)-methylenehydantoin. Imidazolealdehyde (0.1 g.) was mixed with 0.15 g. of hydantoin, 0.26 ml. of pyridine, and one ml. of piperidine and heated at 100° for two minutes. The solids dissolved. After heating, water was added, and then acetic acid to maximum precipitation of the condensation product. The collected precipitate when recrystallized from water gave pale yellow prisms, m.p. 285–287°, very soluble in acetic acid, rather insoluble in ethanol, which can also be employed for recrystallization.

Anal. Calc'd for $C_7H_6N_4O_2$: C, 47.19; H, 3.37; N, 31.46.
Found: C, 47.96; H, 3.56; N, 31.26.

5-Imidazolyl-4(5)-methylenethiohydantoin (0.2 g.) was boiled with a solution of 1 g. of monochloroacetic acid in 3 ml. of water for one and one-half hours. After cooling ammonia was added to maximum precipitation. The precipitate was dried, and recrystallized from water; yellow prisms, m.p. 282–286°, that gave no depression when mixed with a sample of 5-imidazolyl-4(5)-methylenehydantoin.

A sample of 5-imidazolyl-4(5)-methylenehydantoin boiled for a few minutes with acetic anhydride gave a product, m.p. 245°, identical with the diacetyl derivative described above. Mixed melting point 245°.

α-Acetylamino-β-imidazolyl acrylic acid. Imidazolealdehyde (0.4 g.) was mixed with 1 g. of aceturic acid and condensed by heating 20 minutes at 100° with 0.8 g. of sodium acetate and 3.2 g. of acetic anhydride. Water was then added and a solid was collected melting at about 101°. Recrystallized from water, hydrolysis took place and small yellow prisms, m.p. 280°, were obtained, yield 0.45 g. (50 %).

Anal. Calc'd for $C_8H_9N_3O_3$: C, 49.23; H, 4.61; N, 21.53; CH_3CO-, 22.05.
Found: C, 49.91; H, 4.92; N, 21.33; CH_3CO-, 22.44.

Imidazolealdehyde 2,4-dinitrophenylhydrazone. A boiling solution of 0.4 g. of 2,4-dinitrophenylhydrazine in 80 ml. of ethanol was treated with 0.2 g. of imidazolealdehyde. After a few minutes 0.4 ml. of concentrated hydrochloric acid was added; the heating was continued for four minutes and the solution cooled. A precipitate was produced; recrystallized from 50 % acetic acid, it was obtained as orange yellow needles, m.p. 291–292°.

Anal. Calc'd for $C_{10}H_8N_6O_4 \cdot HCl$: C, 38.40; H, 2.88; N, 26.83.
Found: C, 38.72; H, 3.05; N, 26.85.

5-[1-Acetylimidazolyl-4(5)-methylene]-3-acetylcreatinine. (IV). Creatinine (6 g.), 3 g. of imidazolealdehyde, 6 g. of fused sodium acetate, and 24 ml. of acetic anhydride were heated at 135° for 30 minutes. Water was then added, the precipitate collected and recrystallized

from a mixture of acetic acid–acetic anhydride; dark yellow crystals, m.p. 262°, yield 5.2 g. (60%).

Anal. Calc'd for $C_{12}H_{13}N_5O_3$: C, 52.36; H, 4.72; N, 26.41.

Found: C, 52.55; H, 4.87; N, 26.08.

5-[Imidazolyl-4(5)-methyl]hydantoin picrate. (II). 5-[1-Acetylimidazolyl-4(5)-methylene]-1-acetylhydantoin (0.7 g.) was suspended in 7 ml. of water and treated with 7 g. of 3 % sodium amalgam. Solution took place, and with the reduction the solution became almost colorless. After 30 minutes dilute hydrochloric acid was added to *p*H 5 but no precipitate was produced. The solution was then evaporated *in vacuo*, the residue extracted with absolute ethanol, the ethanol evaporated, and the residue dissolved in 7 ml. of water. The calculated amount of picric acid was then added and dissolved by heating. A dark yellow *picrate* was obtained that, upon recrystallization from water saturated with picric acid, had m.p. 210–212°.

Anal. Calc'd for $C_7H_8N_4O_2 \cdot C_6H_3N_3O_7$: C, 38.14; H, 2.68; N, 23.98; N (NO_2), 10.26 (17).

Found: C, 38.72; H, 3.01; N, 23.41; N (NO_2), 10.95.

DL-*Histidine* (III). 5-[1-Acetylimidazolyl-4(5)-methylene]-1-acetylhydantoin (6.6 g.) was suspended in 66 ml. of water and treated with 66 g. of sodium amalgam. After 30 minutes, when the solution was colorless, the mercury and remaining sodium amalgam were separated, the solution was diluted with 27 ml. of water, 60 g. of crystalline barium hydroxide was added, and the mixture was heated to boiling for 12 hours. The barium was then eliminated with sulfuric acid and the new filtrate brought to *p*H 4.4–4.6 with hydrochloric acid. The solution was diluted to 1500 ml. and a warm solution of 40 g. of mercuric chloride in 135 ml. of 96 % ethanol was added. By the addition of sodium carbonate to *p*H 7–7.5 a precipitate was produced that after 24 hours was washed well with water. It was then suspended in 300 ml. of water and the mercury eliminated with hydrogen sulfide. After separation of the mercuric sulfide, the filtrate was decolorized with Norit, concentrated to 15 ml., neutralized with sodium carbonate, and diluted to 100 ml. Then 10.4 g. of picric acid was added and the mixture heated to solution. Upon cooling, *histidine dipicrate* separated. A total of 10 grams (yield, 70%) was obtained, m.p. 105°. Pyman (3) gives m.p. 103°.

5-[Imidazolyl-4(5)methyl]-2-acetylcreatinine picrate. (V). 5-[1-Acetyl-imidazolyl-4(5)-methylene]2-acetylcreatinine (1 g.) was suspended in 10 ml. of water and reduced by the addition of 10 g. of 3% sodium amalgam. Solution of the compound took place and decoloration marked the end of the reaction. After separation of the mercury, the solution was neutralized, the amount of picric acid calculated for the formation of a dipicrate added, and dissolved by heating. Upon cooling, a yellow *picrate* was obtained that recrystallized from water had m.p. 207–210°.

Anal. Calc'd for $C_{10}H_{13}N_5O_2 \cdot C_6H_3N_3O_7$: C, 41.37; H, 3.45; N, 24.03; N (NO_2), 9.05 (17).

Found: C, 41.87; H, 3.59; N, 23.53; N (NO_2), 9.71.

DL-*N-Methylhistidine.* (VI). 5-[1-Acetylimidazolyl-4(5)-methylene]2-acetylcreatinine (5 g.) was suspended in 50 ml. of water and reduced as usual with 50 ml. of sodium amalgam. The solution containing the 5-[imidazolyl-4(5)-methyl]-2-acetylcreatinine was diluted with 20 ml. of water, 45 g. of crystalline barium hydroxide was added and the mixture boiled for 12 hours, keeping the volume constant. The barium was then separated quantitatively, and the washings of the barium sulfate added to the above solution. This solution was concentrated to 50 ml. and 2.25 g. of picric acid was added and dissolved by heating. On cooling, 8.2 g. (yield, 71 %) of a *dipicrate*, m.p. 128°, was obtained. By recrystallization from water a m.p. of 132° was attained. Fargher and Pyman (13) give m.p. 132°.

SUMMARY

1. A new synthesis of DL-histidine and of DL-N-methyl histidine starting from imidazolealdehyde has been described.

2. Some condensation reactions of imidazolealdehyde are described.

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THIAZOLESULFENAMIDES[1]

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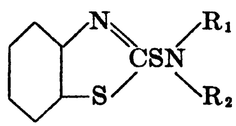
The discovery that benzothiazole-2-thiol is an excellent and inexpensive accelerator for the sulfur vulcanization of rubber (1) has stimulated the study of many types of 1-thiazole-2-thiol derivatives. Among these, some benzothiazolesulfenamides, I, (R_1 and R_2 = hydrogen or hydrocarbon radicals) have been shown to be of outstanding value (2) as delayed-action, self-activating accelerators in both natural and synthetic rubbers.



I

One of these compounds was developed in Germany just before the war as "Vulkacit AZ" ($R_1 = R_2$ = ethyl). A parallel but independent development in this country resulted in the large scale production and use of "Santocure" (R_1 = hydrogen and R_2 = cyclohexyl).

This paper reports the synthesis of thiazolesulfenamides by an improved method which has been developed and extended to include the preparation of many new thiazolesulfenamides of possible interest to the rubber and other industries. A recent review covers the field of the known sulfenic acids and sulfenic acid derivatives very completely (3). The synthesis of sulfenamides from the corresponding sulfenic acids has been impractical because, with few exceptions, these acids are either unknown or very unstable.

Many sulfenyl chlorides and other halides are stable compounds which react with amines as well as sulfenyl thiocyanates to form sulfenamides (5, 6, 7, 8).

$$RSX + R_1R_2NH \rightarrow RSNR_1R_2 + HX$$

Trichloromethylsulfenyl chloride was the first sulfenyl halide to be prepared (4), but others of the aliphatic series have been difficult to obtain with the exception of the triphenylmethyl (5) and the *tert*-butyl (6) sulfenyl halides. The aromatic sulfenyl chlorides, especially the nitrophenyl derivatives are more stable and most sulfenamides have been prepared from these.

Similarly, thiazolesulfenyl halides should react readily to yield the corresponding sulfenamides. This reaction has been reported for a benzothiazolesulfenyl chloride (9), but the product of its reaction with a primary aliphatic amine is a *bis*-benzothiazolesulfenimide, rather than the expected N-monosubstituted benzothiazolesulfenamide.

$$2\,RSX + R_1NH_2 \rightarrow (RS)_2NR_1 + 2HX$$

[1] Presented before the Division of Organic Chemistry at the 109th meeting of the American Chemical Society, Atlantic City, N. J., April, 1946.

Certain thiazolesulfenamides have been prepared by the reaction of metallic thiazolyl mercaptides with the N-chloro derivatives of secondary amines (10).

$$RSM + R_1R_2NX \rightarrow RSNR_1R_2 + MX$$

However, this method of preparation has not been very convenient, especially for industrial use, because of the difficulties involved in the preparation and handling of the N-monochloro derivatives of the more common amines.

Another method available for the preparation of thiazolesulfenamides is the reaction of the corresponding thiazolyl disulfide with ammonia and amines (10, 11).

$$RSSR + 2\ R_1R_2NH \rightarrow RSNR_1R_2 + RSNH_2R_1\ R_2$$

This method is claimed to be of general application. However, although fair yields of thiazolesulfenamides are obtained, only half of the thiazolyl disulfide molecule is utilized in the formation of the corresponding sulfenamide. Furthermore, the sulfenamide must be separated from the substituted ammonium thiazolyl mercaptide also formed in the reaction mixture. This process may be improved by the simultaneous use of an oxidizing agent, and this improvement led to the third and most useful method for the preparation of thiazolesulfenamides.

The new process consists of the direct oxidative condensation of an amine and a metallic thiazolyl mercaptide in aqueous solution (12).

$$RSM + R_1R_2NH + (O) \rightarrow RSNR_1R_2 + MOH$$

The best oxidizing agents from the standpoints of both effectiveness and cost are chlorine and sodium hypochlorite. The other halogens are equally effective and are sometimes more suitable for laboratory preparations. Using chlorine, sodium hypochlorite or iodine as oxidizing agents, suitable reaction conditions have been determined which will give satisfactory yields of thiazolesulfenamides from the joint oxidation of most aliphatic or alicyclic primary or secondary amines with thiazolyl mercaptides.

The usual process utilizes an excess of amine in an aqueous solution containing the sodium salt of the mercaptothiazole together with some additional alkali. The reaction mixture is then stirred during the slow addition of oxidizing agent.

The exact conditions necessary to obtain the highest yield and the purest product from any given amine and thiazolyl mercaptide require a balance between (1) the relative concentrations of the reactants, especially that of the amine, (2) the *p*H of the solution, and (3) the temperature. The effects of these factors may be summarized as follows:

1. *Amine/mercaptide ratio.* An excess of 0.10 to 3 moles of amine above the theoretical quantity is required in order to produce thiazolesulfenamides from thiazolyl mercaptides. Additional amine over the theoretical increases the yield by a mass-action effect, but above a ratio of 3–4 moles of amine to one of mercaptide, this effect becomes negligible.

2. *Alkalinity* (*p*H). The optimum *p*H for the formation of the thiazolesulfen-

amides as determined in the preparation of the N-cyclohexyl- and N-isopropylbenzothiazole-2-sulfenamides is 12.0–12.5 as measured with a Beckman "Type E" lithium-glass electrode and a Beckman *p*H meter. At *p*H values lower than 12.2, 2-benzothiazolyl disulfide is invariably found as an impurity in the product. At *p*H values above 12.5, a pure sulfenamide product is formed but in somewhat lowered yield. In this case, the 2-benzothiazolyl mercaptide is used up in a side reaction forming a soluble product. The most probable side reaction is the oxidation of mercaptide to the water-soluble sodium benzothiazole-2-sulfonate (13), a known reaction in more concentrated solutions at higher temperatures.

The use of sodium hypochlorite as an oxidizing agent produces an increase in the *p*H of the mixture during the course of the reaction, hence acid must be added to control the *p*H within the desirable limits or a lowered yield will result. On the other hand, if a halogen, such as chlorine or iodine is used, the *p*H is lowered during the reaction, and alkali must be added in order to keep the *p*H above the minimum of 12.0. However, it was found possible, when using free halogens as oxidizing agents, to start the reaction with a somewhat higher *p*H (13.0–13.5) without loss in yield or quality of product, providing that the *p*H of the final reaction mixture remained slightly above 12.0. Similarly, using hypochlorite a slightly lower starting *p*H is allowable if the final reaction mixture falls within the most desirable range.

3. *Temperature.* A temperature range of 5–30° generally was found to be satisfactory. Higher temperatures tend to favor the oxidation of mercaptide to sulfonate mentioned above, decreasing the yield of sulfenamide. On the other hand, very low temperatures tend to favor the formation of disulfide impurities in the sulfenamide product.

The balance between these factors lies in using an excess of amine and employing a temperature, *p*H, and amine/mercaptide ratio just above that necessary to keep the disulfide from precipitating.

As an example of the effect of the balance of the factors just discussed, a 96.5% yield of N-cyclohexyl-2-benzothiazolesulfenamide was obtained at room temperatures using either (a), an excess of 0.25 mole of cyclohexylamine while controlling the *p*H at 12.3, or (b), an excess of 3 moles of amine starting with an initial *p*H of 13.1 and allowing the *p*H to fall to 12.5 during the reaction. Chlorine was used as the oxidizing agent in both of these experiments. In general, it was found that 70–95% yields of most thiazolesulfenamides could be obtained by starting with 3–5 moles of amine and 1–1.5 moles of sodium hydroxide per mole of sodium thiazolyl mercaptide, followed by the addition of the oxidizing agent slowly with stirring at 10–20°.

The process is limited to some extent by the insolubility in water and by the ease of oxidation of certain amines. Thus it has been impossible to prepare thiazolesulfenamides from ordinary aromatic amines by this method. However, mercaptides of other sulfhydryl compounds, such as the mercaptothiazolines, thio-*p*-cresol, etc., may be employed in the process as well as the thiazolyl mercaptides.

The so-called "oxidative condensation process" described above, which is

carried out by the addition of oxidizing agent to a mixture of thiazolyl mercaptide and amine, is believed to take place in steps, with the intermediate formation of the thiazolyl disulfide. The probable reactions, starting with a primary alkylamine and oxidizing with either hypochlorite or chlorine are as follows:

1. $$RNH_2 + H_2O \rightarrow RNH_3^+ + OH^-$$

2. $$\begin{cases} \text{(a) } 2\,R_1S^- + Cl_2 \rightarrow R_1SSR_1 \downarrow + 2\,Cl^- \\ \text{(b) } 2\,R_1S^- + OCl^- + H_2O \rightarrow R_1SSR_1 \downarrow + Cl^- + 2\,OH^- \end{cases}$$

3. $$R_1SSR_1 + RNH_3^+ + 2\,OH^- \rightarrow R_1SNHR \downarrow + R_1S^- + 2\,H_2O$$

over-all reaction

$$1. + 2. + 3. \begin{cases} \text{(a) } R_1S^- + RNH_2 + Cl_2 + OH^- \rightarrow R_1SNHR \downarrow + 2\,Cl^- + H_2O \\ \text{(b) } R_1S^- + RNH_2 + OCl^- \rightarrow R_1SNHR \downarrow + Cl^- + OH^- \end{cases}$$

Reactions 1 and 2 proceed very rapidly. As oxidizing agent is added to the reaction mixture, an initial precipitation or cloudiness is observed. If conditions of concentration, pH, and temperature are correct, this initial precipitate disappears as rapidly as formed, and the sulfenamide is produced, first in solution and later with precipitation. However, if the concentrations of amine and mercaptide, pH, or the temperature, individually or collectively, are too low, the thiazolyl disulfide first formed remains as an undesired product from the first of the reaction. This insoluble disulfide will react with excess of the amine in solution (if any) according to the conditions and time of contact. If the conditions are such that this reaction is slow, an undue amount of time may be involved, and the amount of disulfide left at any given time will lower the yield of sulfenamide and necessitate purification of the latter. The reaction of amine with disulfide, reaction 3, appears to be the rate-controlling reaction for the process.

The summation of the three steps [1 + 2 + 3], (a) and (b) indicates the stoichiometry of the over-all process, and shows that alkali will be used up in the process when chlorine is the oxidizing agent, but alkali is formed in the process when hypochlorite is used. This is what actually happens in practice, and the corresponding changes in pH should be taken into account during the reacting period.

In several instances, especially for those reactions involving ammonia and ethylenediamine, it was found advantageous to change the order of addition of the reactants in order to obtain better yields of the desired products. In these reactions, the oxidizing agent, sodium hypochlorite, was added to a concentrated solution of ammonia or amine. To the resulting solution or slurry of chloramine (14) was then added a solution of sodium thiazolyl mercaptide, resulting in the precipitation of the sulfenamide. The mercaptide solution could be added simultaneously with the hypochlorite solution, with good results as long as the hypochlorite addition was kept in advance of the mercaptide.

This "chloroamine process" also proceeds in steps, which may be represented as follows, starting with a primary amine and oxidizing with a hypochlorite solution:

4. $$RNH_2 + H_2O \rightarrow RNH_3^+ + OH^-$$

5. $$RNH_3^+ + OCl^- \rightarrow RNHCl \downarrow + H_2O$$

6. $$R_1S^- + RNHCl \rightarrow R_1SNHR \downarrow + Cl^-$$

Over-all reaction, 4. + 5. + 6.

$$R_1S^- + RNH_2 + OCl^- \rightarrow R_1SNHR + Cl^- + OH^-$$

It is seen that the sum of reactions 4, 5, and 6 is identical to the sum of the steps in the oxidative condensation process 1, 2b, and 3, although the course of the reactions, and the intermediates are quite different. As would be expected, the optimum conditions for the chloroamine process are different from those for the oxidative condensation process, requiring higher concentrations of reactants, lower temperatures, and a higher pH, which is automatically controlled to a certain extent by the optimum conditions for the formation of the chloroamine. These conditions are further compared and discussed in connection with the preparation of thiocarbamylsulfenamide in another communication from this laboratory (15).

The reaction of the chloroamine involves splitting the nitrogen-chlorine bond during the nucleophilic displacement reaction (6) so that the electron pair is retained by the chlorine atom to form chloride ion:

$$R_1{:}\underset{\cdot\cdot}{\overset{\cdot\cdot}{S}}{:}^- \quad + \quad R{:}\underset{\cdot\cdot}{\overset{\overset{\displaystyle H}{\cdot\cdot}}{N}}\,|{:}Cl \rightarrow R_1{:}\underset{\cdot\cdot}{\overset{\cdot\cdot}{S}}{:}^{\delta(-)}\ldots{:}\underset{\underset{\displaystyle R}{\cdot\cdot}}{\overset{\overset{\displaystyle H^{\delta(+)}}{\cdot\cdot}}{N}}\ldots{:}\underset{\cdot\cdot}{\overset{\cdot\cdot}{Cl}}{:}^{\delta(-)} \rightarrow R_1{:}\underset{\cdot\cdot}{\overset{\cdot\cdot}{S}}{:}\underset{\underset{\displaystyle R}{\cdot\cdot}}{\overset{\overset{\displaystyle H}{\cdot\cdot}}{N}}{:} + {:}\underset{\cdot\cdot}{\overset{\cdot\cdot}{Cl}}{:}^-$$

As the chloride ion separates, the electron-deficient nitrogen atoms are satisfied simultaneously, in this case, by sharing with mercaptide ions, $R_1{:}\underset{\cdot\cdot}{\overset{\cdot\cdot}{S}}{:}^-$, which are abundant in the concentrated mercaptide solution, thus forming the sulfenamide.

In the oxidative condensation process, the disulfide is split unsymmetrically, reaction 3, one sulfur atom retaining the electron pair bond, $R_1{:}\underset{\cdot\cdot}{\overset{\cdot\cdot}{S}}|\underset{\cdot\cdot}{\overset{\cdot\cdot}{S}}{:}R_1$, to form a mercaptide ion, $R_1{:}\underset{\cdot\cdot}{\overset{\cdot\cdot}{S}}{:}^-$, and an electron-deficient sulfur, $R_1{:}\underset{\cdot\cdot}{\overset{\cdot\cdot}{S}}^+$, which is satisfied immediately by sharing with ammonium ions, $\left[R{:}\underset{\underset{\displaystyle H}{\cdot\cdot}}{\overset{\overset{\displaystyle H}{\cdot\cdot}}{N}}{:}H\right]^+$ this process requiring that the amine must be in abundant supply, thus forming the sulfenamide. This reaction is exactly analogous to the splitting of disulfides with aqueous caustic, which is believed to proceed according to the following steps:

7. $$2\,R_1{:}\underset{\cdot\cdot}{\overset{\cdot\cdot}{S}}{:}\underset{\cdot\cdot}{\overset{\cdot\cdot}{S}}{:}R_1 + 4\,OH^- \rightarrow 2\,R_1{:}\underset{\cdot\cdot}{\overset{\cdot\cdot}{S}}{:}\underset{\cdot\cdot}{\overset{\cdot\cdot}{O}}{:}^- + 2\,R_1{:}\underset{\cdot\cdot}{\overset{\cdot\cdot}{S}}{:}^- + 2\,H_2O$$

8. $$2\,R_1\,{:}\underset{\cdot\cdot}{\overset{\cdot\cdot}{S}}{:}\underset{\cdot\cdot}{\overset{\cdot\cdot}{O}}{:}^- \rightarrow R_1\,{:}\underset{\cdot\cdot}{\overset{\overset{\displaystyle {:}\overset{\cdot\cdot}{O}{:}}{\cdot\cdot}}{S}}{:}\underset{\cdot\cdot}{\overset{\cdot\cdot}{O}}{:}^- + R_1\,{:}\underset{\cdot\cdot}{\overset{\cdot\cdot}{S}}{:}^-$$

7. + 8. $$2\,R_1{:}\underset{\cdot\cdot}{\overset{\cdot\cdot}{S}}{:}\underset{\cdot\cdot}{\overset{\cdot\cdot}{S}}{:}R_1 + 4\,OH^- \rightarrow R_1{:}\underset{\underset{\displaystyle {:}\underset{\cdot\cdot}{O}{:}}{\cdot\cdot}}{\overset{\cdot\cdot}{S}}{:}\underset{\cdot\cdot}{\overset{\cdot\cdot}{O}}{:}^- + 3\,R_1{:}\underset{\cdot\cdot}{\overset{\cdot\cdot}{S}}{:}^- + 2\,H_2O$$

The sulfenic acid originally formed (7) is believed to rearrange to form mercaptide and sulfenic acid according to reaction 8. The amount of recoverable mercaptide should be 75.5% of the original disulfide, which is the experimental fact in the case of 2-benzothiazolyl disulfide.[2]

At higher temperatures this reaction probably competes with the formation of sulfenamides in the oxidative condensation process, but at lower temperature (0–50°), the electron-deficient sulfur apparently prefers to share with nitrogen rather than with oxygen and forms the sulfenamide exclusively.

The thiazolesulfenamides are in general rather unstable compounds, decomposing spontaneously even when dry, in times varying from a few minutes to several months or years. The decomposition products identified in each case are the disulfide (RSSR) and the substituted ammonium thiazolyl mercaptide. Light and heat accelerate the rate of decomposition. The presence of free alkali also catalyzes the reaction, thus making it necessary to free the products entirely from the alkali of the reaction mixture.

The thiazolesulfenamides are, however, fairly resistant to the action of alkalis as compared with their reactivity toward strong acids. Acidic substances decompose the sulfenamides quickly in aqueous solution or in dry ether with the formation of disulfides and the amine salts of the acids used. Probable intermediates in this reaction are the thiazolesulfenyl chlorides. In several experiments using N-cyclohexylbenzothiazolesulfenamide with hydrogen chloride in dry ether, a small amount of ether-soluble yellow oil was obtained, possibly 2-benzothiazolesulfenyl chloride, which decomposed rapidly at ordinary temperatures forming solid 2-benzothiazolyl disulfide.

The stability of a 2-benzothiazolesulfenamide was found to depend upon the nature of the amine from which it was derived. Primary alkylcarbinamines, RCH_2NH_2, gave low-melting solid, or liquid compounds which decomposed rather rapidly (in a few weeks) under ordinary conditions. The secondary alkylcarbinamines, R_2CHNH_2, gave thiazolesulfenamides which melted higher for compounds of equal molecular weights than those from the primary carbinamines, and they were more stable under ordinary conditions. In the one instance tried, a tertiary carbinamine, R_3CNH_2 (*tert*-amylamine) yielded a sulfenamide of higher melting point and greater stability than the corresponding secondary and primary compounds. Unsaturation or branching of the chain beyond the α-carbon atom appeared to make little difference in the stability. Substitution with a phenyl group, (*e.g.* the sulfenamide from benzylamine), or other negative substituents, (*e.g.* hydroxyl) appeared to stabilize the resulting sulfenamide.

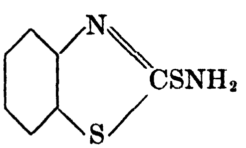
Secondary alkyl amines gave liquid sulfenamides whose stability was inter-

[2] Unpublished results obtained by Dr. B. J. Humphrey of this laboratory. Dr. Humphrey utilized a new method for the determination of benzothiazole-2-thiol, which is to be published. In the development of this method it was found that the use of barium hydroxide gave more consistent and reliable results than sodium hydroxide in dissolving the sample. The results here referred to were obtained by treatment of benzothiazolyl disulfide with barium hydroxide, followed by determination of the benzothiazole-2-thiol in the solution.

mediate between the primary and the tertiary carbinamine compounds. The corresponding sulfenamides prepared from cyclohexylamine and from heterocyclic amines such as piperidine, piperazine, and morpholine, had higher melting points and better stability than the groups of compounds from both secondary carbinamines and secondary alkylamines. The *bis*-substituted thiazolesulfenamides from piperazine and ethylenediamine were both relatively high-melting and stable.

The sulfenamides from the alkylthiazole-2-thiols were less stable than those from the benzothiazole-2-thiols and the thiazoline-2-sulfenamides were still less stable.

Benzothiazole-2-sulfenamide, II, reacted readily with phenylisocyanate forming N-phenylcarbamylbenzothiazole-2-sulfenamide, III. Reaction of the N-cyclohexylbenzothiazole-2-sulfenamide with phenyl isocyanate produced only N-phenyl-N′-cyclohexylurea. Furthermore, 2-benzothiazolyl disulfide was the product of the reaction of isothiocyanates with 2-benzothiazolesulfenamide. An acetyl derivative, IV, of the benzothiazolesulfenamide was formed, together with some disulfide, by the action of acetic anhydride in the presence of sodium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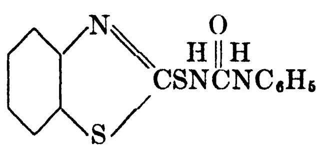
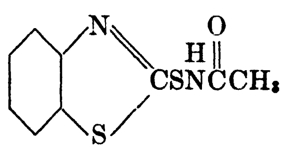

III


IV

acetate. Acid chlorides (acetyl, benzoyl, *p*-nitrobenzoyl) and 2,4-dinitrochlorobenzene yielded only the disulfide. Phthalyl chloride yielded phthalimide and disulfide.

Both thiazoline-2-sulfenamide and benzothiazole-2-sulfenamide reacted with amines to form substituted sulfenamides. In fact this reaction was used to es-

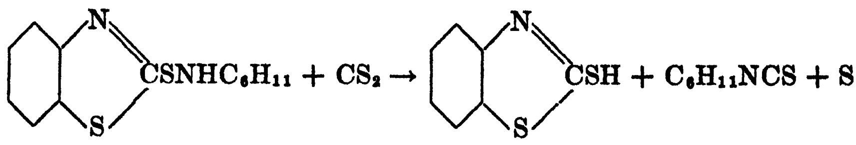
$$RSNH_2 + \begin{matrix} R_1 \\ \quad\diagdown \\ \quad NH \\ \quad\diagup \\ R_2 \end{matrix} \rightarrow RSN\begin{matrix} R_1 \\ \diagup \\ \\ \diagdown \\ R_2 \end{matrix} + NH_3$$

tablish the identity of thiazoline-2-sulfenamide which was too unstable to retain in a pure state for analysis. These amine exchange reactions are convenient for the preparation of sulfenamides otherwise difficult to prepare, *e.g.*, from long chain and other water-insoluble amines, such as dodecyl- and hexadecenylamine. Similar reactions have been described by Howland (16).

Benzaldehyde and formaldehyde reacted with benzothiazole-2-sulfenamide II. Acetone did not react with II, but did react with N-cyclohexylbenzothiazole-2-sulfenamide. The products were not identified.

Carbon disulfide was without effect on 2-benzothiazolesulfenamide, but

reacted with the N-cyclohexyl derivative with the formation of benzothiazole-2-thiol and cyclohexyl isothiocyanate.



This reaction offers a unique and convenient new method for the preparation of aliphatic and substituted aliphatic isothiocyanates.

The sulfenamides were readily reduced by strong reducing agents such as sodium dithionite (hyposulfite) solution to the corresponding thiazolyl mercaptan and amine.

EXPERIMENTAL

PREPARATION OF SULFENAMIDES

Four different modifications which were used in the preparation of the sulfenamides have been identified in Table I by the use of Roman numerals I through IV inclusive. Some of the compounds were prepared by several different modifications. However, only the conditions of the particular modification which gave the best results are recorded in Table I. In most of the preparations considerable excesses of amine (3–20 moles) were used. The use of excess amine ensured that the desired sulfenamide would be obtained, but this excess probably would not be necessary if optimum conditions of temperature, concentration, etc., were determined. These optimum conditions have been worked out in a few cases and in each case it was found that only a very small excess of amine was necessary under the best conditions of preparation.

In general, the compounds were purified for analysis by recrystallization several times from petroleum ether. In a few instances, ether or mixtures of ether with other solvents were used. The compounds were found to be soluble in all of the ordinary organic solvents, and they were much more soluble than the dibenzothiazolyl disulfide which was frequently the chief impurity from which they were separated.

The ordinary Kjeldahl procedure for nitrogen analysis is not applicable to this type of compound. For the nitrogen analyses reported, a convenient modification of the Friedrich micro-Kjeldahl procedure (17) was used.

It is interesting to note that in the preparation of the compounds from ethylenediamine and from piperazine, there was the possibility for the formation of both mono- and di-substituted compounds. In both cases the disubstituted (*bis*) compounds were separated. In certain preparations of these compounds there was evidence for the formation of some monosubstituted compound, but this was not separated and identified. There was only one possibility, of course, in the preparation from morpholine.

An example of each of the four identified procedures employed is given below:

I. *Simultaneous addition of oxidizing agent and alkali mercaptide to an aqueous solution of amine. Preparation of benzothiazole-2-sulfenamide.* A clear solution was prepared by dissolving 16.7 g. (0.1 mole) of purified benzothiazole-2-thiol in 75 cc. of water containing 4.0 g. (0.1 mole) of sodium hydroxide. This solution and 75 cc. of a 10% sodium hypochlorite solution were dropped slowly at equal rates into 300 cc. of conc'd ammonium hydroxide (28%, sp. gr., 0.90). The mixture was cooled in an ice-bath (5–10°) and strongly stirred throughout the addition. The sulfenamide formed as a white bulky solid which occupied considerable volume and made the stirring less effective. The precipitate was washed with cold water until free from alkali. The product was completely soluble in ether but after drying four days at room temperature, it contained a very small ether-insoluble fraction of 2-benzothiazolyl disulfide; yield, 17 g., (93.5%). The product was crystallized from a

chloroform-petroleum ether mixture, m.p. 127–128°, forming a red liquid which decomposed at slightly higher temperatures.

II. *Oxidative condensation. Use of iodine in aqueous potassium iodide solution as an oxidizing agent. Preparation of N-cyclohexylbenzothiazole-2-sulfenamide.* A clear aqueous solution was prepared containing 10.0 g. (0.06 mole) of benzothiazole-2-thiol, 4.8 g. (0.12 mole) of sodium hydroxide, and 18 g. (0.18 mole) of cyclohexylamine in a total volume of 250 cc. To this solution at room temperature was added, drop by drop with stirring over a period of one hour, 15.3 g. (0.12 mole) of iodine dissolved in 200 cc. of water containing 16.5 g. of potassium iodide. As the iodine solution made contact with the clear reaction mixture at first, a region of turbidity appeared and then vanished. After about one-tenth of the iodine solution had been added, the sulfenamide began to separate in the form of white crystal plates. The product was washed with water until free from alkali, and air-dried at a temperature not exceeding 50°; yield 15.2 g. (96%). It was completely soluble in ether, petroleum ether, and alcohol, indicating the absence of disulfide. It was crystallized from ether or petroleum ether, m.p. 102°.

III. *Oxidative condensation. use of chlorine (air-diluted) as an oxidizing agent. Preparation of N-cyclohexylbenzothiazole-2-sulfenamide.* A solution was prepared containing 167 g. (1.0 mole) of benzothiazole-2-thiol, 100 g. (2.5 moles) of sodium hydroxide, and 245 g. (2.5 moles) of cyclohexylamine in a volume of 5000 cc. A mixture of chlorine with air, (about 6–8 parts of air to one of chlorine), was introduced into the mixture through four small-bore glass nozzles arranged in parallel. Rapid stirring was used throughout the reaction. The temperature varied from 25° to 32° and the *p*H was lowered from 13.1 to 12.5 during the reaction, which was run to completion, that is, until no benzothiazole-2-thiol was precipitated from a filtered test sample on acidification. The time required was 4–5 hours. The first product redissolved in the reaction mixture. After about fifteen minutes, glistening white crystals of the sulfenamide began to separate. Towards the end of the reaction, the precipitate became more granular and a light tan in color. The product was washed free of alkali with cold water and dried at temperatures below 50°; yield, 254 g. (96.5%). The product contained about 0.5% of ether-insoluble material. One crystallization from ether or petroleum ether yielded pure white crystals, m.p. 102°.

Exactly the same results were obtained by using less initial sodium hydroxide and controlling the *p*H of the solution between 12.3–12.5 by addition of sodium hydroxide solution from a burette, drop by drop, during the reaction. The yield of light tan product was 255 g. (96.5%). In both experiments, the initial moist material was completely soluble in ether but developed about 0.5–0.6% ether-insoluble material during the drying. Crystallized as above, m.p. 102°.

IV. *Oxidative condensation. Use of sodium hypochlorite as an oxidizing agent. Preparation of N-cyclohexylbenzothiazole-2-sulfenamide.* A solution of 16.7 g. (0.1 mole) of benzothiazole-2-thiol and 4.0 g. (0.1 mole) of sodium hydroxide was made in about 100 cc. of water. To this was added 12.4 g. (0.125 mole) of cyclohexylamine, and the whole solution was diluted to 250 cc. The initial *p*H of this solution was 12.4. It was cooled to 10°, causing the formation of some crystals, presumably the cyclohexylammonium salt of benzothiazole-2-thiol. Solutions of about 10% sodium hypochloride and about 4.1 *N* sulfuric acid were added, drop by drop, simultaneously from two burettes at such rates that the *p*H of the solution was kept between 12.2–12.5 throughout the reaction. The mixture was stirred vigorously and kept at 9.5–10.5°. Addition was continued until there was no free benzothiazole-2-thiol left in solution, as found by acidification of a small amount of filtrate. The pure white crystalline precipitate was filtered, washed thoroughly with water and dried; yield, 22.1 g. (83.8%). Before drying, the product was entirely ether-soluble, but it developed 2.25% insoluble disulfide during drying; m.p. 98–102°.

In another experiment, similar results were obtained by using more amine (0.35 mole) and adding the sodium hypochlorite very slowly with stirring at room temperature (25°). No attempt was made to control the *p*H in this experiment. The product was dried at room temperature; m.p. 100–102° without further purification, yield, 82.5%.

TABLE I
Thiazole-2-sulfenamides

	Prep. Method	Yield, %	Mole Ratio Amine to Thiazole	Reaction Temp., °C.	M.P., °C.	Analysis S Calc'd	Analysis S Found	Analysis N Calc'd	Analysis N Found
I. THIAZOLE-2-SULFENAMIDE									
N-Cyclohexyl-	I	—	5:1	25–30	52–53	29.9	29.7	13.1	13.1
II. BENZOTHIAZOLE-2-SULFENAMIDE									
Unsubstituted	I	94	—	5–10	127–128	35.18	35.25	—	—
N-Methyl-	III	68	5:1	Room T.	Liq.	—	—	—	—
N,N-Dimethyl-	II	39	5:1	0–20	Liq.	—	—	—	—
N-Ethyl-	II	79	20:1	Room T.	55–57	30.49	30.80	13.32	12.97
N,N-Diethyl-	III	55	4:1	Room T.	Liq.	—	—	—	—
N-*n*-Propyl-	II	77	5:1	Room T.	32–33	28.58	28.47	12.49	12.35
N-Isopropyl-	III	82	3:1	Room T.	93–94	28.58	28.54	12.49	12.46
N-*n*-Butyl-	II	64	10:1	Room T.	35–37	11.75	11.15	—	—
N,N-Di-*n*-butyl-[a]	II	—	4:1	Room T.	Liq.	—	—	—	—
N-(1-Methylpropyl)-	II	70	5:1	Room T.	49–50	26.90	27.04	11.75	11.68
N-(1-Methylbutyl)-	II	96	5:1	8–11	58–60	25.41	25.38	11.10	11.19
N-(2,2-Dimethylpropyl)-	II	—	5:1	Room T.	80–82	25.41	25.60	11.10	11.50
N-(1,3-Dimethylbutyl)-	II	71	5:1	5–6	52–54	24.07	24.15	10.52	10.31
N,N-Di-*n*-amyl-[b]	II	37	4:1	0–20	Liq.	—	—	—	—
N-(2-Hydroxyethyl)-	II	—	10:1	Room T.	94–95	—	—	12.10	11.90
N-Methallyl-	II	76	12:1	Room T.	64–66	27.13	26.97	11.85	11.76
N-Cyclohexyl-	II	96	2.5:1	25–32	102	24.25	24.55	—	—
N-Benzyl-	II	95	4:1	Room T.	117	23.54	23.90	10.29	10.00
N,N′-Ethylene-*bis*-	IV	26.5	4:1	—	125–126	—	—	—	—
N-Cyclopentamethylene-	III	60	6:1	Room T.	80	—	—	—	—
N-Oxadiethylene-(from morpholine)	II	86	10:1	Room T.	85–86	25.41	25.65	11.10	10.65
N,N′-Diethylene-*bis*-(from piperazine)	II	96	5:1	0–20	190–192	30.78	30.65	13.45	13.42
N-Furfuryl-	(IV)	52	1.25:1	0–10	103–104	24.1	24.1	10.7	10.6
N-Thenyl-	(IV)	—	1.25:1	0–10	105–106	—	—	10.1	9.8
N-(2-Methyl-2-hydroxypropyl)-	(IV)	16	1.25:1	0–10	108–109	11.0	10.7	25.1	24.7

III. 6-NITROBENZOTHIAZOLE-2-SULFENAMIDE									
N-Cyclohexyl-	II	—	—	—	119	20.72	20.90	13.58	13.50
IV. 4-METHYLTHIAZOLE-2-SULFENAMIDE									
N-Cyclohexyl-	II	73	3.5:1	8–10	49–50	—	—	—	—
V. 4-ETHYLTHIAZOLE-2-SULFENAMIDE									
N-Cyclohexyl-	II	77	3:1	0–20	65–68	—	—	—	—
VI. 4,5-DIMETHYLTHIAZOLE-2-SULFENAMIDE									
N-Isopropyl	II	80	10:1	8–10	62–63	—	—	—	—
N-(1-Methylpropyl)-	II	72	5:1	Room T.	51–52	—	—	—	—
N-(1-Methylbutyl)-	II	56	5:1	Room T.	40–42	—	—	—	—
N-(1,3-Dimethylbutyl)-	II	51	5:1	5–7	Liq.	—	—	—	—
N-Cyclohexyl-	II	95	4:1	Room T.	92–94	—	—	—	—
N,N'-Diethylene-*bis*-(from piperazine)	II	—	7.5:1	Room T.	154	34.42	34.70	15.04	15.43
VII. TETRAHYDROBENZOTHIAZOLE-2-SULFENAMIDE									
N-Isopropyl-	II	53	10:1	Room T.	Liq.	—	—	—	—
N-(1-Methylbutyl)-	II	—	5:1	Room T.	Liq.	—	—	10.9	10.7
N-Cyclohexyl-	II	—	3:1	5–10	100–103	—	—	—	—
N-Benzyl-	II	—	5:1	Room T.	Liq.	—	—	10.1	9.9
VIII. THIAZOLINE-2-SULFENAMIDE									
Unsubstituted[c]	I	—	6:1	0	49–51	—	—	—	—
N-Isopropyl-	III	47	1.25:1	0	28–28.5	36.38	36.52	15.89	15.92
N-(1-Methylbutyl)-	III	70	1.25:1	0	Liq.	—	—	—	—
N-Cyclohexyl-	II	83	3:1	Room T.		29.64	29.60	12.95	13.00

[a] A dioxane-water mixture was used as a reaction medium instead of water because of the water insolubility of di-*n*-butylamine. [b] In this case alcohol was used as an auxiliary solvent because of the low water solubility of di-*n*-amylamine. [c] The identity of thiazoline-2-sulfenamide was proven by reaction with cyclohexylamine which formed the N-cyclohexyl derivative.

REACTIONS OF THIAZOLESULFENAMIDES

N-Phenylcarbamylbenzothiazole-2-sulfenamide. III. To 5.0 g. (0.0275 mole) of benzothiazole-2-sulfenamide was added 10.0 g. (0.084 mole) of phenyl isocyanate. The mixture was warmed gently to start the reaction which then took place rapidly, and cooling was necessary to prevent it from becoming too violent. The reaction product was washed with ether, extracted with benzene to remove 2-benzothiazolyl disulfide, and the residue was crystallized several times from boiling alcohol. Pink crystalline plates; m.p., 208–209°, yield, 39%.

Anal. Calc'd for $C_{14}H_{11}N_3OS_2$: N, 13.94; S, 21.28.
Found: N, 13.60, 13.75; S, 21.13.

N-Acetylbenzothiazole-2-sulfenamide. IV. To 20.0 g. (0.196 mole) of acetic anhydride was added 2.0 g. (0.0242 mole) of fused sodium acetate and 4.0 g. (0.022 mole) of benzothiazole-2-sulfenamide. The mixture was allowed to stand about fifteen hours at 30°. A small amount of water was added to hydrolyze the acetic anhydride, and the 2-benzothiazolyl disulfide was then filtered off. Further dilution of the filtrate with water precipitated a low-melting solid, which, after several recrystallizations from ether yielded the pure acetyl derivative, m.p. 135–136°, yield, 30%.

Anal. Calc'd for $C_9H_8N_2OS_2$: N, 12.49; S, 28.59.
Found: N, 12.48, 12.53; S, 28.57, 28.73.

Reaction of N-cyclohexylbenzothiazole-2-sulfenamide with phenyl isocyanate. To an ether solution of 10.0 g. (0.038 mole) of N-cyclohexyl-2-benzothiazolesulfenamide was added 9.0 g. (0.075 mole) of phenyl isocyanate. There was no evidence of immediate reaction, but on standing fifteen hours at 35–40°, the reaction mixture solidified. The product was washed with ether, and crystallized from benzene and then from toluene. The white crystals, m.p. 181–182°, proved to be N-phenyl-N′-cyclohexylurea. A mixture melting point determination with an authentic sample (m.p. 179–181°) prepared from phenyl isocyanate and cyclohexylamine was 179–181°. Yield, 42.7%. An additional 24% yield of crude material was recovered from the ether filtrate.

Anal. Calc'd for $C_{20}H_{21}N_3OS_2$: N, 12.85. Found: N, 12.40.

Action of carbon disulfide on N-cyclohexylbenzothiazole-2-sulfenamide. Five grams of the N-cyclohexylbenzothiazole-2-sulfenamide was mixed with 50 cc. of carbon disulfide. Solution was practically immediate, and for ten minutes there was no evidence of reaction. A crystalline product, 2 g., then precipitated with a slight evolution of heat. The product, m.p. 179°, was soluble in alkali and when mixed with pure benzothiazole-2-thiol the melting point was not depressed. Evaporation of the solvent left a liquid with a strong odor, and a small amount of solid. The liquid reacted with cyclohexylamine to give N,N′-dicyclohexylthiourea which was identified by the melting point, 179°, and mixture melting point. The liquid product was, therefore, cyclohexyl isothiocyanate. Free sulfur probably was formed but was not identified. A sample of the liquid from another similar preparation was distilled; b.p. 81–83°/3, n_D^{30} 1.5384.

The reaction of amines with thiazole- and thiazoline-sulfenamides. A small amount of benzothiazole-2-sulfenamide was dissolved in isopropylamine and the solution allowed to stand for three hours. The solid residue had m.p. 92–93°. A mixture melting point with a sample of N-isopropylbenzothiazole-2-sulfenamide showed no depression.

A similar experiment involving thiazoline-2-sulfenamide and cyclohexylamine yielded a product which was identified by melting point, and mixture melting point as N-cyclohexylthiazoline-2-sulfenamide. In this case the reaction was taken as proof of the identity of the very unstable thiazoline-2-sulfenamide.

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SUMMARY

A general method has been developed for the preparation of thiazolesulfenamides by the oxidation of 2-mercaptothiazoles in the presence of amines with halogen oxidizing agents. This method has been extended to the preparation of N-substituted sulfenamides from ammonia; primary, secondary, and heterocyclic amines; and from 2-mercaptothiazoline and 2-mercaptoalkylthiazoles as well as from 2-mercaptobenzothiazoles. Some of the chemical reactions and the factors affecting the stability of the thiazole sulfenamides have been discussed briefly.

AKRON 17, OHIO

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THIOCARBAMYLSULFENAMIDES[1]

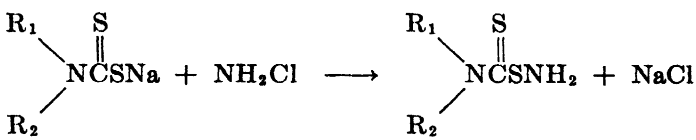
GEORGE E. P. SMITH, JR., GLEN ALLIGER, EDWARD L. CARR, AND KENNETH C. YOUNG

Received January 2, 1948

Certain thiazole-2-thiols, dithiocarbamates, and their related compounds are important accelerators for the sulfur vulcanization of rubber and rubber-like polymers. Experimental work on the preparation of thiocarbamylsulfenamides was undertaken as a natural extension of earlier studies of the corresponding thiazole derivatives (1, 2).

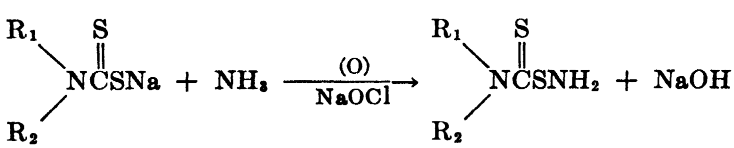
Unsubstituted N,N-dialkylthiocarbamylsulfenamides have been prepared by the reaction of monochloroamine and sodium N,N-dialkyldithiocarbamates (3).

1.



Independently of the work described in the above patents, it was found by us that these compounds may be prepared by addition of sodium dithiocarbamates and a 10% solution of sodium hypochlorite at approximately equimolecular rates to an excess of concentrated ammonia. It is possible that monochloroamine is formed as an intermediate in this reaction.

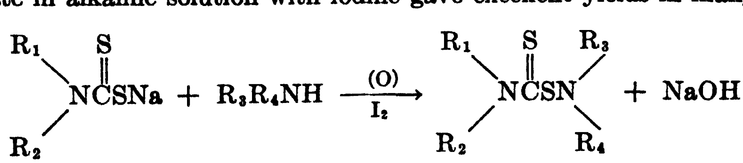
2.



Several of the methods which were used for the preparation of the substituted thiazolesulfenamides (1) have been found to be applicable to the preparation of the corresponding substituted thiocarbamyl analogs (3).

Oxidative condensation of an aliphatic amine with a N,N-dialkyldithiocarbamate in alkaline solution with iodine gave excellent yields in many cases.

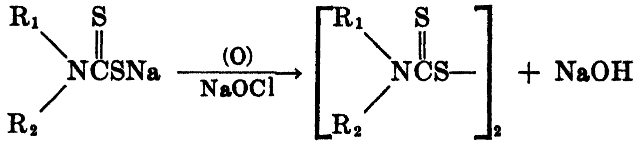
3.



This equation represents the reaction previously found to be the most generally applicable to the preparation of thiazolesulfenamides (1, 2). The iodine was used in a solution of potassium iodide. Sodium hypochlorite could be used instead of

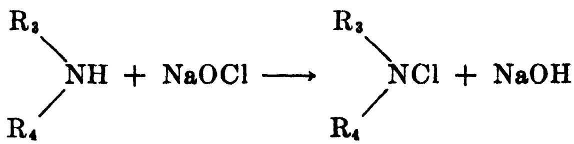
[1] Presented before the Division of Organic Chemistry at the 110th meeting of the American Chemical Society, Chicago, Ill., Sept., 1946.

iodine, but with this oxidizing agent the product contained an appreciable amount of tetraalkylthiuram disulfide in addition to the desired sulfenamide.

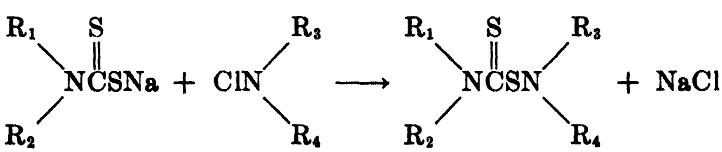
4. 

In the previous work the formation of thiazolyl disulfides was also found to be a side reaction in the preparation of the thiazole sulfenamides when either sodium hypochlorite or chlorine was used as an oxidizing agent, but this could be minimized or prevented entirely by the use of excess amine and the maintenance of the *p*H between 12.0 and 13.0 (1, 4). Such was not the case for the thiocarbamyl compounds. Using chlorine or sodium hypochlorite, thiuram disulfides were formed as impurities in the sulfenamide product at any *p*H from 10–13 and in spite of large excesses of amine.

Sodium hypochlorite could be successfully used, however, if the N-monochloroamine were first prepared (1, 5),

5. 

and then allowed to react with a sodium N,N-dialkyldithiocarbamate (1, 3, 6).

6. 

In several cases excellent yields were obtained by this method. Furthermore, it was possible to adjust conditions so that little or no thiuram disulfide was formed as an impurity in the product.

For the preparation of N,N-diethylthiocarbamyl-N′-cyclohexylsulfenamide a variation of the above process which involved simultaneous addition of sodium N,N-diethyldithiocarbamate and sodium hypochlorite solutions proved successful, provided that a slight excess of hypochlorite was maintained in the reaction mixture during the addition. It is probable that, under these conditions, N-monochlorocyclohexylamine was formed as an intermediate.

With regard to the probable steps involved in the reaction it has been postulated in a previous communication from this laboratory (1) that, when an oxidizing agent is added to a mixture of an amine and a metal mercaptide, the formation of the sulfenamide may be represented as follows:

7. $$RNH_2 + H_2O \rightarrow RNH_3^+ + OH^-$$

8. $$2\,R_1S^- + (O) + H_2O \rightarrow R_1S{-}SR_1 + 2\,OH^-$$

9. $$R_1S{-}SR_1 + RNH_3^+ + 2\,OH^- \rightarrow R_1S{-}NHR + R_1S^- + 2\,H_2O$$

Evidence that supports this proposal in preference to the assumption that a N-chloroamine is an intermediate is as follows:

1. In the presence of amines and oxidizing agents, disulfides may be converted to sulfenamides.

2. Oxidizing agents other than halogens and hypohalites can be used to oxidize mixtures of amines and metal mercaptides to sulfenamides (2).

3. In the case of thiazole sulfenamides careful adjustment of *p*H together with the use of excess amine was necessary to prevent the occurrence of thiazolyl disulfides in the final product (1, 4).

During the work with thiocarbamylsulfenamides a number of confirmatory observations were made.

1. Sodium hypochloride was suitably used for the preparation of thiocarbamylsulfenamides only by preparing the N-monochloroamine as an intermediate.

2. The conditions found optimum for the preparation of thiocarbamylsulfenamides *via* the N-monochloroamines were quite different from those necessary when using direct oxidative condensation of a metal mercaptide and an amine by iodine.

3. In the case of N,N-diethylthiocarbamyl-N′-cyclohexylsulfenamide, in order to obtain a good yield free from tetraethylthiuram disulfide, it was necessary to use a temperature above 25° and a 2.5-mole excess of cyclohexylamine in the direct oxidative condensation process. Indeed, when the reaction was run at a lower temperature (5–20°) the product formed contained an appreciable amount of disulfide, but merely heating the reaction mixture completed the conversion to the sulfenamide. On the other hand, when N-monochlorocyclohexylamine was used as an intermediate, there was no evidence of disufide formation at any reaction temperature from 0 to 40°, although a much better yield was obtained at lower temperatures.

In the joint oxidative condensation reaction when iodine was used as the oxidizing agent, it was necessary to use as much as 50% excess if temperatures above 25° were used. This was probably due to loss of iodine in the formation of iodate. In general, temperatures in the range of 25–50° were found suitable. Four to five moles of amine per mole of dithiocarbamate were necessary for good yields in most cases, although as little as 2.5 moles were used in a few instances.

In the chloroamine process, the N-monochloroamines were prepared by addition of sodium hypochlorite (2.5 *M*) to the primary amines at temperatures of 10° or below. As previously demonstrated by Coleman (5) it was necessary to maintain a 10–15% excess of amine in order to prevent the formation of dichloroamines. Those of low molecular weight were slightly soluble whereas those having five or more carbon atoms were relatively insoluble in the aqueous reaction mixtures.

In most cases the sodium N,N-dialkyldithiocarbamate was added to the suspension as prepared above without separation of the chloroamine. The sulfenamide products were then obtained as water-insoluble liquids or crystalline solids. However, as an alternative method, the chloroamine could be extracted with ether, and the reaction carried out by addition of the alkali dithiocarbamate,

TABLE I

THIOCARBAMYLSULFENAMIDES

SULFENAMIDE	YIELD, %	PREP. METHOD[a]	MOLE RATIO AMINE TO DITHIOCARBAMATE	TEMP. REACTION, °C.	M.P., °C.	ANALYSIS S Calc'd	ANALYSIS S Found	ANALYSIS N Calc'd	ANALYSIS N Found
N,N-Dimethylthiocarbamylsulfenamide									
1. Unsubstituted	73.5	II	45:1	0–10	69–71	—	—	—	—
2. N′-Ethyl	—	I	5:1	25–30	35–37	—	—	—	—
3. N′-Cyclohexyl	—	I	5:1	25–30	23–24	—	—	12.8	12.6
4. N′-Pentamethylene	80	I	4:1	50–30	77–79	31.30	31.38	—	—
N,N-Diethylthiocarbamylsulfenamide									
5. N′,N′-Diethyl	77.6	I	5:1	40–25	Liquid	29.1	29.90	—	—
6. N′-Cyclohexyl	55 (80)	I (III)	2.5:1 (1.25/1)	25 (0–5)	64–65	26.00	26.20	11.40	11.35
N,N-Diallylthiocarbamylsulfenamide									
7. N′-*n*-Butyl	53	III	1.25:1	0–10	Liquid	—	—	11.5	11.0
N,N-Dimethallylthiocarbamylsulfenamide									
8. N′-*n*-Butyl	32	III	1.25:1	0–10	Liquid	—	—	10.3	10.0
N-Phenyl-N-Methylthiocarbamylsulfenamide									
9. N-Isopropyl	—	IV	1:1	30–40	72–73	26.6	26.0	11.6	11.5
10. N-Pentamethylene	—	IV	1:1	30–40	82–83	24.0	23.8	10.5	10.3
N-Tetramethylenethiocarbamylsulfenamide									
11. N′-*n*-Butyl	71	I	5:1	25–30	Liquid	—	—	12.8	12.9
12. N′-Pentamethylene	70	I	5:1	25–30	103–103.5	—	—	12.1	12.3
13. N′-Benzyl	57	I	5:1	25–30	93–94	25.4	25.7	11.1	10.8

N-Pentamethylenethiocarbamylsulfenamide									
14. Unsubstituted	—	II	30:1	0–10	54–56	—	—	—	—
15. N′-Isopropyl	42 (45)	I (III)	5:1 (2/1)	40–30 (0–5)	52–53	29.36	29.51	12.83	13.10
16. N′-(1,3-Dimethylbutyl)	—	I	4:1	30–25	25–27	26.00	26.37	—	—
17. N′-Cyclohexyl	2.6 (75)	I (III)	3:1 (1.25/1)	4–10	75–75.5	24.81	24.82	10.84	10.95
18. N′-Pentamethylene	92 (38)	I (III)	3:1 (1.25/1)	40–35	100–102	26.02	26.04	11.36	11.25
N-Oxadiethylenethiocarbamylsulfenamide (from Morpholine)									
19. N′-Isopropyl	31	I	5:1	25	80–81	—	—	—	—
20. N′-Cyclohexyl	50	I	3:1	15	85–86	—	—	—	—

[a] I. Iodine oxidation of an amine-alkali dithiocarbamate mixture.
II. Simultaneous addition of sodium hypochlorite and an alkali dithiocarbamate to the aqueous amine solution.
III. Addition of a solution of an alkali dithiocarbamate to an aqueous suspension of the N-monochloroamine.
IV. Reaction of solid alkali dithiocarbamate with an ether solution of the monochloroamine.

either as the dry salt or in aqueous solution, to the ether solution of the chloroamine. In this case the sulfenamide was in the ether phase at the end of the reaction.

The reaction of hypochlorites with primary amines to form N-monochloro primary amines is easily reversed. For instance Coleman (5) found that shaking an ether solution of a N-monochloro primary amine with aqueous acid solutions regenerated the amine. Chapin (7) discovered that, in aqueous solution, the monochloro, dichloro, and free primary amines were in equilibrium, the relative

TABLE II (a)

SULFENAMIDES FROM N-MONOCHLOROCYCLOHEXYLAMINE AND VARIOUS MERCAPTIDES

MERCAPTIDE	SULFENAMIDE	YIELD, %	M.P., °C.	REFERENCE, M.P., °C.
Sodium N,N-diethyldithiocarbamate	N,N-Diethylthiocarbamyl-N′-cyclohexylsulfenamide	80	64.5–65.5	(See Table I)
Sodium benzothiazole-2-mercaptide	N-Cyclohexylbenzothiazole-2-sulfenamide	86	98 –101	102
Sodium 4,5-dimethylthiazole-2-mercaptide	N-Cyclohexyl-4,5-dimethylthiazole-2-sulfenamide	82	93 –94	92–94

TABLE II (b)

SULFENAMIDES FROM THE SODIUM SALT OF 2-MERCAPTOBENZOTHIAZOLE AND VARIOUS CHLOROAMINES

N-MONOCHLOROAMINE	SULFENAMIDE	YIELD, %	M.P., °C.	REFERENCE, M.P., °C.
N-Monochloroisopropylamine	N-Isopropylbenzothiazole-2-sulfenamide	40	90–93	93–94
N-Monochloro-*sec*-butylamine	N-*sec*-Butylbenzothiazole-2-sulfenamide	70	49–49.5	49–50
N-Monochloro-(1-methylbutyl)amine	N-(1-Methylbutyl)benzothiazole-2-sulfenamide	86	55–58	58–60

The references for melting points of the thiazolesulfenamides in this table are given in Ref. (1).

quantity of each depending on the *p*H of the solution. At *p*H above 8.5, pure monochloroamine was found.

If, therefore, one adds sodium hypochlorite to an excess of primary amine, the reaction may be represented as follows:

$$RNH_2 + Cl^+ \rightleftharpoons RNHCl + H^+ \quad (10)$$

Depending on the molecular weight of the amine, one would expect the completeness of chloroamine formation to depend on the *p*H, and on the solubility of the chloroamine. It follows that the yield of sulfenamide obtained by addition of alkali mercaptide to an aqueous suspension of N-monochloro primary amine prepared from sodium hypochlorite and amine would depend on these same factors of *p*H and solubility.

Actually it was found that the yield of sulfenamide increased

1. As the concentration of reactants was increased, *i.e.* as the amount of the aqueous phase was decreased.
2. As the temperature was decreased.
3. By saturation of the aqueous phase with salt.
4. By use of excess amine or chloroamine.

For given conditions of temperature and concentration, the yield of sulfenamide should be independent of the mercaptide used, being about the same in each case for a given N-monochloroamine and increasing as the molecular weight of the chloroamine was increased. The results summarized in Tables II (a) and II (b) support this assumption. Table II (a) gives the yields of sulfenamide which resulted from the reaction, under identical conditions, of N-monochlorocyclohexylamine with three mercaptides. Table II (b) shows the results of the reaction of sodium benzothiazole-2-mercaptide with three different N-monochloroamines, the conditions being the same for each case.

The effect of *p*H was difficult to determine since at a *p*H lower than 13.0 local over-heating from the heat of reaction initiated decomposition of the chloroamine. However, in one preparation of N,N-diethylthiocarbamyl-N′-cyclohexylsulfenamide, the *p*H was maintained at 12.0–12.5 by periodic additions of sulfuric acid. The yield was much lower and the product less pure than that obtained from preparations where the *p*H was 13.0 to 13.5. Attempts to control the *p*H at a value lower than 13.0 by dilution of the reaction mixture also decreased the yield. This may be ascribed to a shifting of the equilibrium of reaction 10 to the left.

The above experimental facts support the formulation of the chloramine process in the following steps as discussed in reference (1):

$$\text{11.}\qquad RNH_2 + H_2O \rightarrow RNH_3^+ + OH^-$$

$$\text{12.}\qquad RNH_3^+ + OCl^- \rightarrow R\overset{H}{N}Cl + H_2O$$

$$\text{13.}\qquad R_1S^- + R\overset{H}{N}Cl \rightarrow R_1S\overset{H}{N}R + Cl^-$$

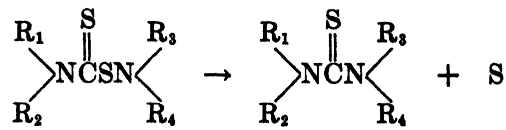
The optimum conditions as determined for the chloroamine and oxidative condensation processes may be summarized as follows:

	OXIDATIVE CONDENSATION PROCESS	CHLOROAMINE PROCESS
Temperature	0–50°	−10° to +10°
*p*H	12.0–12.5	13
Concentration of mercaptide	*Ca.* 0.5 molar	2 to 3 molar
Amine/mercaptide ratio	1.25 to 5	1.10 to 1.25

These conditions are approximately those required for the optimum reaction of disulfide with amine in the oxidative condensation process and for the optimum formation of chloroamine in the chloroamine process.

The thiocarbamylsulfenamides are readily decomposed by heating or long

standing. The products of such decompositions were found to be thioureas formed from the sulfenamides by loss of sulfur.

14. 

This is in contrast to the decomposition of thiazole-2-sulfenamides which usually decompose with the formation of thiazolyl disulfides.

The thiocarbamylsulfenamides are readily split by aqueous acids to give products which were not identified.

EXPERIMENTAL

To prepare the sodium N,N-dialkyldithiocarbamates equimolecular quantities of sodium hydroxide and the secondary amine were dissolved in water and the carbon disulfide added slowly with stirring. The solution was cooled meanwhile. Yields were assumed to be theoretical. Members of the series prepared from high molecular weight (*e.g.*, from di-2-ethyl-*n*-hexyl) amines formed slowly and it was necessary to heat to 60° to complete the reactions. If the dithiocarbamate separated from solution, alcohol was used to increase the solubility. The concentration was generally in the range 0.3 to 2.0 molar.

The iodine-potassium iodide solution was about 0.5 molar with respect to iodine. Water-insoluble amines such as dibutylamine were brought into solution by addition of alcohol to the reaction mixture.

N-Monochloroamines were prepared by adding a 10–15% solution of sodium hypochlorite to the amine at 10° or below. It was necessary to use a 10–15% excess of amine in preparing a N-monochloro primary amine in order to prevent the formation of any dichloroamine. The monochloroamines were separated as oils or crystalline solids. The solubility of the monochloroamines decreased as the molecular weight of the monochloroamine increased.

A number of the thiocarbamylsulfenamides prepared proved to be liquids at room temperature. The sensitivity of these compounds to acid materials and to heat eliminated extraction with aqueous acids or distillation as means of purification. However, the appearance and solubility as well as the method of preparation indicated them to be sulfenamides. These liquid materials included N,N-diethylthiocarbamylsulfenamide; the N′-isopropyl and N′-cyclohexyl derivatives of N,N-dimethylthiocarbamylsulfenamide; the N′-isopropyl, N′-(1-methylbutyl), and N′-cyclopentamethylene derivatives of N,N-diethylthiocarbamylsulfenamide; the N′,N′-di-*n*-butyl and N′-cyclopentamethylene derivatives of N,N-di-*n*-butylthiocarbamylsulfenamide; the N′-(1-methylbutyl)-N-cyclopentamethylenethiocarbamylsulfenamide; the N′-(1-methylpropyl), and N′-(1-methylbutyl) derivatives of N-oxadiethylenethiocarbamylsulfenamide (from morpholine). The N′-isopropyl derivatives of N,N-di-(2-ethylhexyl)thiocarbamylsulfenamide and N,N-di-*n*-laurylthiocarbamylsulfenamide were waxy materials melting at 55–60° and 150–165° respectively. They were obtained in small amounts but were not definitely characterized.

All of the crystalline thiocarbamylsulfenamides, together with methods of preparation and properties, are listed in Table I. A few typical procedures are given below.

N,N-Dimethylthiocarbamylsulfenamide. An aqueous solution of sodium N,N-dimethyldithiocarbamate was prepared from 4 g. (0.1 mole) of sodium hydroxide, 18 g. (0.1 mole) of an aqueous solution of dimethylamine (25%), and 7.6 g. (0.1 mole) of carbon disulfide. The solution was diluted to a volume of 75 ml. This solution and 75 ml. of a 10% sodium hypochlorite solution were added dropwise at equal rates to 300 ml. of cold conc'd aqueous ammonia. After a time a perfectly white, flocculent precipitate began to form. When the addition of dithiocarbamate and hypochlorite solution was completed, the solid material was dried and weighed; yield, 10 g. (73.5%), m.p. 69–71°, (uncorr.).

N,N-DIETHYLTHIOCARBAMYL-N'-CYCLOHEXYLSULFENAMIDE

(*a*) *Use of iodine as oxidizing agent.* A solution of sodium N,N-diethyldithiocarbamate was prepared from 146 g. (2.0 moles) of diethylamine, 80 g. (2.0 moles) of sodium hydroxide, and 152 g. (2.0 moles) of carbon disulfide in 800 ml. of water. To this solution was added 800 g. (8 moles) of cyclohexylamine. Next, at a temperature of 15–20°, was added slowly over a period of 1½ hours a solution of 508 g. (2.0 moles) of iodine and 500 g. of potassium iodide in 2 liters of water. After about half of the iodine solution had been added the temperature was raised to 31° and the addition completed. The reaction mixture was diluted to 8 liters and the precipitate washed and dried. Yield 395 g., (82%), m.p., 62–65°, (uncorr.).

(*b*) *Use of sodium hypochlorite as an oxidizing agent. First method.* In 350 ml. of an aqueous solution of 35.6 g. (0.36 moles) of cyclohexylamine and 56.4 g. (0.33 mole) of sodium, N,N-diethyldithiocarbamate were placed a Beckman "Type E" glass electrode and a calomel electrode connected to a Beckman *p*H meter. The *p*H of the solution was adjusted to 12.0 by addition of sulfuric acid solution (40%). After bringing the reaction mixture to 30°, it was maintained at that temperature while 0.39 mole of sodium hypochlorite (230 ml., 1.71 *M*) was added slowly, with simultaneous addition of acid to maintain the *p*H at 12.0–12.5.

After all of the hypochlorite solution had been added the oily solid which had separated was collected. Treatment with petroleum ether served to separate the less soluble tetraethylthiuram disulfide, 27 g. (55%), m.p. 69–71°, from the N,N-diethylthiocarbamyl-N'-cyclohexylsulfenamide, 15.7 g. (19%), m.p. 56–59°.

(*c*) *Use of sodium hypochlorite as an oxidizing agent. Second method.* To 37.6 g. (0.38 mole) of cyclohexylamine were added simultaneously 0.38 mole of sodium hypochlorite (216 ml., 1.78 *M*) and 0.33 mole of sodium N,N-diethyldithiocarbamate (192 ml., 1.7 *M* solution) the relative rate of addition being such that the hypochlorite added was always slightly in excess of the dithiocarbamate. Meanwhile, the temperature was maintained at 5–8° and the mixture stirred vigorously. When the addition was completed the reaction mixture was stirred for one hour. The white crystalline material which had precipitated was washed, dried, and weighed. Yield, 44.4 g. (54%); m.p. 62.5–64.5° (uncorr.).

(*d*) *Use of N-monochlorocyclohexylamine.* To 34.5 g. (0.35 mole) of cyclohexylamine was added 0.32 mole of sodium hypochlorite (179 ml., 1.79 *M*) the temperature being maintained at 5–10°. The N-monochlorocyclohexylamine separated as a pure white crystalline solid. A portion was washed five times with ice-water and dried on a porous plate in a vacuum desiccator for two hours. Analysis for positive chlorine by the thiosulfate method gave the following results:

Calc'd for $C_6H_{12}ClN$: Cl^+, 26.53. Found: Cl^+, 26.93.

To 0.32 mole of the monochloroamine so prepared but not separated from the reaction mixture was added slowly, and with stirring at a temperature of 5°, 0.30 mole of sodium N,N-diethyldithiocarbamate (158 ml., 1.9 *M*). The reaction mixture was allowed to come to room temperature overnight and the white precipitate dried. Yield, 59 g., (80%); m.p. 59–64°. After one recrystallization from petroleum ether, m.p. 64–65.5° (uncorr.).

N-Cyclopentamethylenethiocarbamyl-N'-cyclopentamethylenesulfenamide. A solution of sodium cyclopentamethylenedithiocarbamate (0.47 mole) was prepared from 40 g. of piperidine, 35.8 g. of carbon disulfide, and 18.8 g. of sodium hydroxide in water. A clear solution was obtained by diluting to a volume of 200 ml. and heating to 45–50°.

To this solution was added 3.76 moles of piperidine and then, slowly and with stirring, 119.6 g. (0.47 mole) of iodine dissolved in a solution of 120 g. of potassium iodide in one liter of water. The temperature of the reaction mixture was initially 45°. The iodine-potassium iodide solution was added at such a rate that the temperature fell slowly and was 35° when the addition had been completed. The white crystalline precipitate was washed well and dried. Yield, 105 g., (91.5%). After one recrystallization from petroleum ether, m.p. 100° (uncorr.).

N-Oxadiethylenethiocarbamyl-N'-isopropylsulfenamide. An aqueous solution of 0.227

mole of sodium N-oxadiethylenedithiocarbamate was prepared in the usual way from 19.8 g. of morpholine, 17.3 g. of carbon disulfide, 9.1 g. of sodium hydroxide, and water. This solution was then diluted to a volume of 500 ml. and 67 g. (1.13 moles) of isopropylamine was added. To the resulting solution was added slowly and with stirring an aqueous solution (400 ml.) of 57.7 g. (0.27 mole) of iodine and 58 g. of potassium iodide. The reaction proceeded smoothly at room temperature. For a short time the fine white precipitate, which formed as the iodine contacted the solution, redissolved immediately. Later a permanent crystalline precipitate began to form. This white solid was washed thoroughly and dried. Yield, 15.8 g., (31.5%); m.p. 79–80° (uncorr.).

N-sec-Butylbenzothiazole-2-sulfenamide. To 35.3 ml. (0.35 mole) of *sec*-butylamine was added with stirring 0.30 moles (166.6 ml., 1.8 *M*) of sodium hypochlorite. Meanwhile, the temperature was maintained at 0 to −5°. To the suspension of N-monochloro-*sec*-butylamine so formed was added a solution of 0.30 mole of sodium 2-benzothiazolylmercaptide in 100 ml. of water, the temperature being maintained at 0 to −5° as before. The solid which separated was dried. Yield, 49 g., (70%). Recrystallized from carbon tetrachloride, 49–49.5° (uncorr.).

Decomposition of thiocarbamylsulfenamides. A sample of N-cyclopentamethylenethiocarbamyl-N′-cyclopentamethylenesulfenamide decomposed after several months storage. The decomposition product was a brown oil. Extraction with alcohol left a residue which proved to be mainly sulfur. The soluble portion, after recrystallization, melted at 57.5–58.5°. A mixture melting point with a known sample of N,N′-dipentamethylenethiourea, m.p. 55.5–57°, melted at 55–57°, (uncorr.).

Anal. Calc'd for $C_{11}H_{20}N_2S$: S, 15.10; N, 13.18.
Found: S, 15.29; N, 12.6.

A sample of N-cyclohexyl-N′-pentamethylenethiocarbamylsulfenamide decomposed on standing. Recrystallization of the residue first from alcohol and water and then from gasoline yielded a compound which melted at 128–130°. A mixture melting point with an authentic sample of N-cyclohexyl-N′-pentamethylenethiourea prepared from cyclohexyl isothiocyanate and piperidine, m.p. 129–131°, showed no depression.

An attempt to prepare a thiocarbamylsulfenamide by oxidative condensation of cyclohexylamine and the sodium dithiocarbamate derived from N-*n*-butyl-2-methylpiperazine produced an oil, presumably the desired sulfenamide, which decomposed after standing a day. Recrystallization of the residue from ether-petroleum ether, and then from alcohol-water yielded a material melting at 88–89°. Analysis of this compound indicated it to be N-cyclohexyl-N′-(N-*n*-butyl-2-methylpiperazyl)thiourea.

Anal. Calc'd for $C_{16}H_{31}N_3S$: N, 14.14. Found: N, 14.21.

A sample of N,N-dimethylthiocarbamyl-N′-cyclohexylsulfenamide was decomposed by heating on a hot plate at 80–100°. Recrystallization from toluene and alcohol yielded a material, m.p. 178–180°, which showed no lowering of melting point when mixed with a known sample of *N,N′-dicyclohexylthiourea*. The formation of the symmetrically substituted thiourea from the unsymmetrically substituted thiocarbamylsulfenamide indicates that an amine exchange reaction took place, with volatilization of dimethylamine and its replacement by cyclohexylamine.

SUMMARY

Methods previously used for the preparation of thiazolesulfenamides have been used in preparing the thiocarbamylsulfenamides. The use of N-monochloro primary amines as intermediates in the preparation of both thiazole- and thiocarbamyl-sulfenamides has been developed.

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[CONTRIBUTION FROM THE CHEMICAL AND PHYSICAL RESEARCH LABORATORIES OF THE FIRESTONE TIRE AND RUBBER COMPANY]

REACTIONS OF MONO- AND DI-AMINES WITH CARBON DISULFIDE. I. N,N′-DIALKYLETHYLENEDIAMINE-CARBON DISULFIDE REACTIONS[1]

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The literature is replete with reactions of dialkylmonoamines and carbon disulfide; the products are dialkylammonium salts of dialkyldithiocarbamic acids (I) and may be oxidized to thiuram disulfides (II). These compounds are used widely in the rubber industry as vulcanization accelerators. More recently Smith, Alliger, Carr, and Young (1) of this laboratory have shown that, under certain conditions, the oxidation of dialkyldithiocarbamates in the presence of primary or secondary amines may produce thiocarbamylsulfenamides (III). The decomposition of this type of compound by loss of sulfur results in an N,N′-disubstituted thiourea (IV).

However, analogous reactions of N,N′-dialkyldiamines with carbon disulfide have received only scant attention and the purpose of this investigation was to study this field of chemistry.

It was found that, in general, the reactions of N,N′-dialkylethylenediamines with carbon disulfide follow the same pattern as similar reactions in the dialkylmonoamine series. However, in the diamine series the products are cyclic by virtue of the ethylene chain which links the nitrogen atoms. The analogies between reactions of mono- and di-amines with carbon disulfide are summarized in Chart I; compounds possessing related structures bear the same number with the "A" series representing the cyclic types.

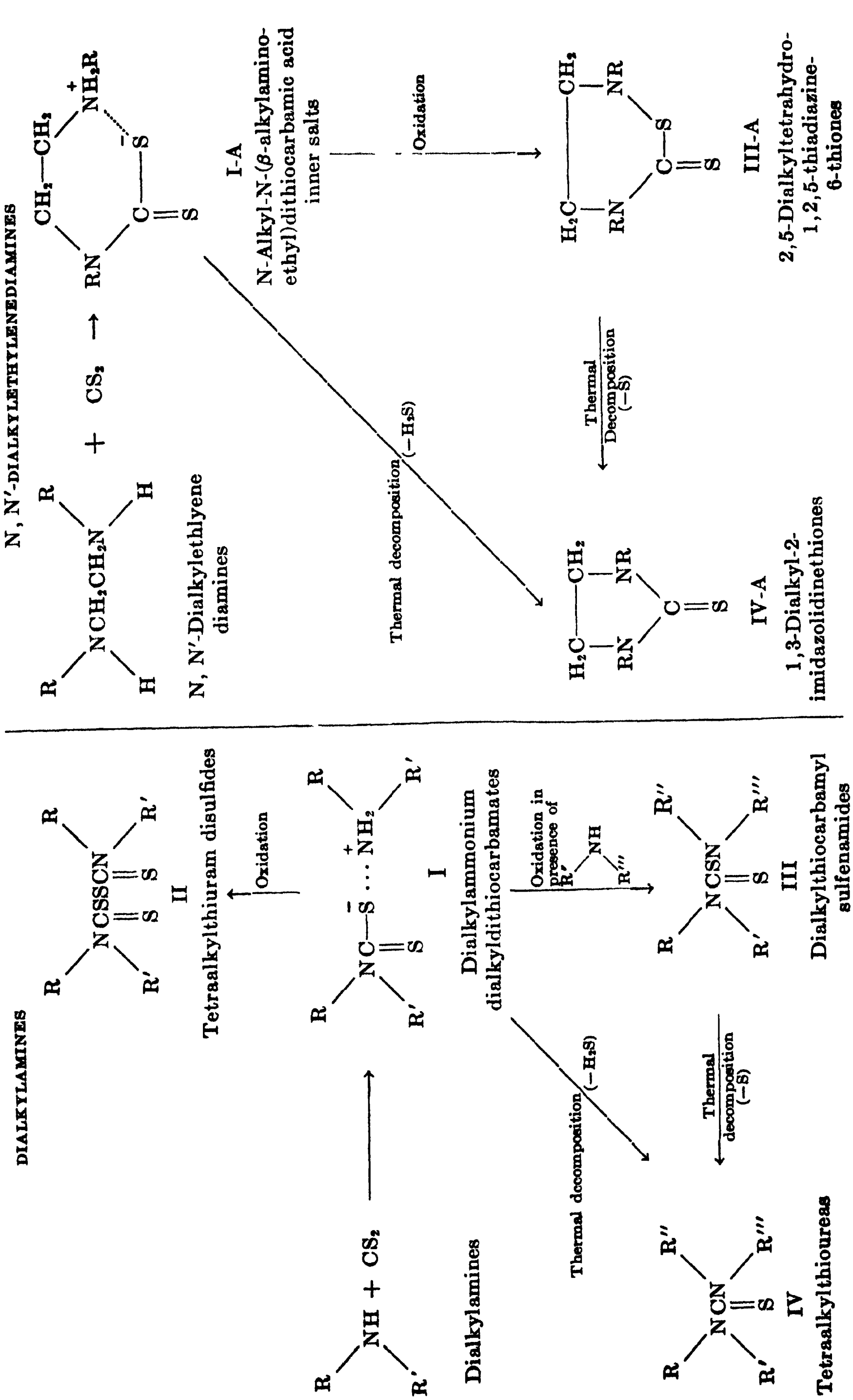
The reaction of ethylenediamine and carbon disulfide was first reported by Hofmann (2) who obtained a product shown to be N-(β-aminoethyl)dithiocarbamic acid (I-A, R = H). He thermally decomposed this acid and obtained hydrogen sulfide and 2-imidazolidinethione (IV-A, R = H). Subsequently these reactions were extended to N-substituted ethylenediamines by Ristenpart (3), Lob (4), van Alphen (5), Sebrell and Clifford, (6, 7), Zienty and Thielke (8), Zienty (9), Newman (10), and Schinzel and Benoit (11).

Using similar reactions we have prepared other 1,3-dialkyl-2-imidazolidinethiones from the thermal decomposition of the corresponding N-alkyl-N-(β-alkylaminoethyl)dithiocarbamic acid inner salts (I-A). Furthermore, it was found that the dithiocarbamic acid inner salts could be oxidized to a new type of compound, the tetrahydro-1,2,5-thiadiazine-6-thiones (III-A), and these new compounds likewise could be thermally decomposed to the same 2-imidazolidinethiones. The new heterocyclic compounds, the tetrahydro-1,2,5-thiadiazines, may be considered to be cyclic thiocarbamylsulfenamides, and their mode of

[1] Presented before the Division of Organic Chemistry at the 110th meeting of the American Chemical Society, Chicago, Ill., Sept., 1946.

CHART I

SUMMARY OF AMINE-CARBON DISULFIDE REACTIONS



formation is analogous to the formation of the open chain thiocarbamylsulfenamides (III) from the dialkylammonium dithiocarbamates (I) (1). Fisher-Hirschfelder-Taylor models show that the six-membered thiadiazine ring is strain-free, but lacks some of the symmetry and stability of the five-membered imidazolidine ring.

It is interesting to note that by analogy with the oxidation of the dialkyldithiocarbamates, the oxidation of the β-alkylaminoethyldithiocarbamic acid inner salts (I-A) could have taken either one of two courses, namely, (a) the formation of a thiuram disulfide from two molecules of acid inner salt or, (b) the intramolecular oxidation to a cyclic thiocarbamylsulfenamide. The latter was a possibility because of the proximity of the mercapto and β-amino groups in the same molecule. The molecular weight values of the products from iodine oxidation of the inner salts indicated that reaction (b) occurred in preference to reaction (a). Analogous to the loss of hydrogen sulfide on thermal decomposition of the dithiocarbamic acid inner salts (I-A), their oxidation products, the tetrahydro-1,2,5-thiadiazine-6-thiones (III-A) readily decomposed with the loss of the ring sulfur leaving 2-imidazolidinethiones (IV-A). The stability of the tetrahydrothiadiazine ring appeared to be related to the size of the alkyl substituent, R. If R was cyclohexyl, the compound could be stored for several weeks without decomposition. However, when R was isopropyl, the pure white compound developed a yellow coloration within several days, probably caused by the formation of free sulfur. Attempts to prepare the ethyl substituted compound resulted chiefly in IV-A and sulfur; only a low yield of the desired thiadiazine product was obtained.

In the monoamine series, the thiocarbamylsulfenamides decompose thermally in an analogous manner to yield substituted thioureas (1). The thermal decomposition of substituted ammonium dithiocarbamates also is assumed to give the same substituted thioureas, although this has been reported only for a dithiocarbamate from a primary amine (13).

EXPERIMENTAL

Preparation of N,N'-dialkylethylenediamines. The N,N-dialkylethylenediamines were prepared by the reaction of ethylene dichloride with primary amines. The alkyl substituents were ethyl, isopropyl, *n*-butyl, *sec*-amyl, cyclohexyl, and 2-ethylhexyl. These diamines were colorless to slightly yellow liquids and all except the *sec*-amyl and 2-ethylhexyl compounds rapidly absorbed water from the air to form solid hydrates.

The general procedure was the same in each case and the preparation of the butyl derivative is given as an example: A mixture of 1.5 moles of ethylene dichloride and 6.6 moles of *n*-butylamine in a 1200-ml. steel bomb was heated electrically. At 104° the temperature suddenly rose to 204°. After cooling, the reaction product, a mushy liquid, was made alkaline with 40% aqueous sodium hydroxide solution, filtered, and the organic layer in the filtrate distilled through a 6-inch Vigreux column. After recovery of excess butylamine the desired product distilled at 92°/4 mm.; yield, 130 g. (50%).

Reactions between ethylene dichloride and amines boiling above 90° were performed in a round-bottom flask equipped with stirrer, reflux condenser, and dropping-funnel. The dichloride was added slowly to the amine at 90–120°. The product was recovered from the reaction mixture as described above.

The N,N'-dialkylethylenediamines which were highly water-soluble, *e.g.*, the diethyl

TABLE I

N,N'DIALKYLETHYLENEDIAMINES, THEIR CARBON DISULFIDE REACTION PRODUCTS, N-ALKYL-N-(β-ALKYLAMINOETHYL)DITHIOCARBAMIC ACIDS (I-A) AND THERMAL DECOMPOSITION PRODUCTS, 1,3-DIALKYL-2-IMIDAZOLIDINETHIONES (IV-A)

R in formulas I-A, III-A and IV-A	N,N'-Dialkylethylenediamine b.p., °C. (uncorr.)/mm.	Dithiocarbamic acid (I-A)					1,3-Dialkyl-2-imidazolidinethione (IV-A)				
		Decomposition Temperature, °C. (corr.)	Analyses				Properties	Analyses			
			Calc'd		Found			Calc'd		Found	
			N	S	N	S		N	S	N	S
Ethyl	150–154/733[b] 65.5/35	157.0–157.4 (white solid)	14.55	33.34	14.7	33.2	m.p., 62.2° (corr.)	17.70	20.26	17.7	20.0
Isopropyl	84/37	153.8–154.4 (white solid)	12.71	29.09	12.8	28.9	m.p. 86.4° (corr.)	15.03	17.20	15.0	17.55
n-Butyl	92/4[c, d]	(white solid)	—	—	—	—	b.p. 144–149°/1[d] n_D^{25} 1.5267	13.07	14.96	13.13	15.18
1-Methylbutyl	86–87/2	(oily viscous liquid)	—	—	—	—	b.p., 149–151°/1 n_D^{25} 1.5203	11.55	13.22	11.65	—
Cyclohexyl	134–136/3[e, f]	166.5–169[e] (white solid)	9.32	21.34	9.7	—	m.p., 226.2° (corr.)[e]	10.51	12.03	10.7	12.6
2-Ethylhexyl	121.5–124/0.5	(oily viscous liquid)	—	—	—	—	b.p., 177–178°/1 n_D^{25} 1.5070	8.58	9.82	8.77	9.69

[a] The sample in a m.p. tube was immersed in a bath approximately 10° below the decomposition temperature. The bath was then heated so that the temperature rose 2° per minute. [b] Schneider (12) reported b.p. 149–150°. [c] Sebrell and Clifford (6) reported b.p. 185–187°/3, probably a misprint in U.S. Patent 1,948,317 (1934). [d] Zienty (9) reported b.p. of diamine, 110–111°/8, decomposition of the acid at 135–136°, and b.p. of 2-imidazolidinethione, 183–184°/8. [e] Zienty and Thielke(8) reported b.p. of diamine 184–186°/25, decomposition of acid at 167–168°, and m.p. of 2-imidazolidinethione, 225–226°. [f] Clifford (7) reported b.p. 136–147°/2.

and diisopropyl derivatives, could be separated from water in improved yields by azeotropic distillation using benzene or toluene as an entrainer (14).

Preparation of N-alkyl-N-(β-alkylaminoethyl)dithiocarbamic acid inner salts (I-A). When carbon disulfide was added slowly to the benzene or acetone solutions of the N,N'-dialkylethylenediamines, the highly exothermic formation of the N-alkyl-N-(β-alkylaminoethyl)dithiocarbamic acid inner salts (I-A) occurred spontaneously. The amyl- and 2-ethylhexyl-substituted compounds failed to separate from solution; evaporation of the solvent in each case left a viscous yellow-orange oil which did not crystallize. The other acid salts precipitated in the reaction mixture as white powders and three of these were characterized (Table I).

An example is the preparation of the compound in which each of the alkyl groups is isopropyl: A solution of 0.5 mole (72 g.) of N,N'-diisopropylethylenediamine in 500 cc. of acetone was cooled to 10°. This was stirred vigorously while 0.53 mole (40 g.) of carbon disulfide in 40 cc. of acetone was added dropwise. A white precipitate soon formed and external cooling was necessary to keep the temperature below 15°. After complete addition, the precipitate was filtered and washed with acetone and ether. Yield, 96 g. (90%) of a white powder (Table I).

TABLE II

PROPERTIES OF 2,5-DIALKYLTETRAHYDRO-1,2,5-THIADIAZINE-6-THIONES (III-A)

R IN FORMULA (III-A)	M.P., °C. (corr.).	MOLECULAR WEIGHT			ANALYSES			
		Calc'd for Thiuram disulfide	Calc'd for Tetrahydro-thiadiazine-thione	Found[a]	Calc'd		Found	
					N	S	N	S
Ethyl	62.0–62.5[b]	382.6	190.3	197	14.71	33.69	14.9	33.9
Isopropyl	104.8–105.0	438.8	218.4	214	12.82	29.32	13.2	29.6
Cyclohexyl	138.8–139.6	599.0	298.5	299	9.41	21.48	9.8	21.7

[a] Determined by the cryoscopic method in benzene. [b] Mixture m.p. of this compound with 1,3-diethyl-2-imidazolidinethione (m.p. 62.2°) was 42–50°, thereby establishing the non-identity of the two closely related compounds.

The compounds shown in Table I were insoluble in the usual organic solvents, but could be purified by solution in ammonia water followed by volatilization of the ammonia at room temperature.

Thermal decomposition of N-alkyl-N-(β-alkylaminoethyl)dithiocarbamic acids (I-A) to 1,3-dialkyl-2-imidazolidinethiones (IV-A). A few grams of the dithiocarbamic acid inner salt was heated in a test tube to slightly above its decomposition temperature until evolution of hydrogen sulfide ceased. The loss of hydrogen sulfide occurred at a fairly definite temperature that is, about 160–170°, although this varied a few degrees with rate of heating and particle size (Table I). The residue containing the corresponding 2-imidazolidinethione, (IV-A), was recrystallized from acetone, ether, or alcohol to constant melting point. Liquid products (alkyl groups = butyl, amyl, and 2-ethylhexyl) were distilled under reduced pressure.

Oxidation of N-alkyl-N-(β-alkylaminoethyl)dithiocarbamic acids (I-A) to 2,5-dialkyltetrahydro-1,2,5-thiadiazine-6-thiones (III-A). Example; R = isopropyl. A solution of 0.4 mole (88 g.) of N-isopropyl-N-(β-isopropylaminoethyl)dithiocarbamic acid in 500 cc. of 1.4 *N* aqueous sodium hydroxide solution was stirred vigorously while aqueous iodine-potassium iodide solution was added dropwise. After precipitation was complete, the product was filtered, dried, and dissolved in acetone. The clear acetone solution was evaporated almost to dryness after which the pale yellow crystals were filtered. Recrystallization from benzene gave 62 g. (71%) of white needles, m.p. 104.8–105.0° (corr.).

Thermal decomposition of 2,5-dialkyltetrahydro-1,2,5-thiadiazine-6-thiones (III-A) to 1,3-dialkyl-2-imidazolidinethiones (IV-A). A few grams of the thiadiazinethione (III-A) in a test tube was heated gently until condensation of sulfur at the mouth of the tube no longer occurred. The residue, containing the corresponding 2-imidazolidinethione, (IV-A), was purified by recrystallization or distillation. Identifications of the products were made by obtaining mixture melting points without lowering, with authentic samples, or by comparing the boiling points and refractive indices of the liquids with those of authentic samples.

SUMMARY

1. A series of N-alkyl-N-(β-alkylaminoethyl)dithiocarbamic acid inner salts was prepared from N,N′ dialkylethylenediamines and carbon disulfide. Thermal-decomposition products of these salts were hydrogen sulfide and 1,3-dialkyl-2-imidazolidinethiones.

2. Halogen oxidation of these acids gave a series of new compounds, 2,5-dialkyltetrahydro-1,2,5-thiadiazine-6-thiones. These new heterocyclic compounds decomposed thermally to produce sulfur and 1,3-dialkyl-2-imidazolidinethiones identical to those produced from the dithiocarbamic acid inner salts.

AKRON 17, OHIO

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[CONTRIBUTION FROM THE CHEMICAL AND PHYSICAL RESEARCH LABORATORIES OF THE FIRESTONE TIRE AND RUBBER COMPANY]

REACTIONS OF MONO- AND DI-AMINES WITH CARBON DISULFIDE. II. METHYLENEDIAMINE AND IMIDAZOLIDINE-CARBON DISULFIDE REACTIONS[1]

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The analogy between dialkylmonoamine-carbon disulfide and the homologous N,N′-dialkyldiamine-carbon disulfide reactions was discussed in Part I. We will show that a parallelism also is found between the dialkylmonoamine-formaldehyde-carbon disulfide and the N,N′-dialkyldiamine-formaldehyde-carbon disulfide reactions. These have been summarized in Chart I; as in Part I, the compounds with related structures have the same number with the "A" series representing the cyclic types.

Dialkylamine-aldehyde-carbon disulfide products have been patented (1, 2, 3) as accelerators for the vulcanization of rubber, although the patents contain no suggestion of molecular structures of the reaction products.

Three methods are available for the synthesis of amine-aldehyde-carbon disulfide accelerators. For example, we have found that the compound obtained from methylene-*bis*-piperidine (I, R and R′ = cyclopentamethylene) and carbon disulfide is identical with the compound prepared by Levi (4) from piperidinium N,N-cyclopentamethylenedithiocarbamate (III, R and R′ = cyclopentamethylene) and formaldehyde. Furthermore, we have prepared the same compound from the dithiocarbamate (III) and piperidinomethanol. This would indicate that the order of addition of formaldehyde and carbon disulfide to the amine does not affect the nature of the final product.

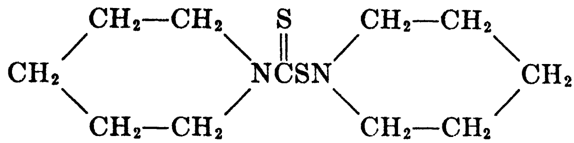
The third method, which involves the use of an alkylaminomethanol, also makes possible the synthesis of the same type of compound in which the N and N′ alkyl groups are dissimilar. The reaction of piperidinomethanol with morpholinium N,N-oxadiethylenedithiocarbamate and with dicyclohexylammonium N,N-dicyclohexyldithiocarbamate resulted in products having dissimilar N,N′-alkyl substituents. These also were found to have activity in accelerating the vulcanization of rubber.

The structure of the above compounds, which result from the three methods of preparation just described, has not been clearly elucidated. Levi proposed an electrovalent, salt type of structure for his product, namely, methylenepiperidinium N,N-cyclopentamethylenedithiocarbamate (II-alternate, R and R′ = cyclopentamethylene). However, there is also the possibility that the methylene group can act as a purely covalent link between the dithiocarbamic acid and amine radicals thereby forming a dithioester, N′,N′-dialkylaminomethyl N,N-dialkyldithiocarbamate (II). In fact similar compounds have been patented by

[1] Presented before the Division of Organic Chemistry at the 110th meeting of the American Chemical Society, Chicago, Ill., Sept., 1946.

Sloan (5) as vulcanization accelerators but he did not disclose their method of preparation.

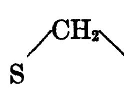
Conclusive chemical evidence for establishing the ester (II) or salt (II-alternate) structure is lacking. However, the physical behavior of this type of compound substantiates the plausibility of II rather than II-alternate. The basis of proposing an ester structure (II) lies in observations on electrical conductivity, solubility, and melting point. The conductivities of 0.01 M solutions of three compounds in nitrobenzene were determined[2]; these were II or II-alternate (R and R′ = cyclopentamethylene), III (R and R′ = cyclopentamethylene), and N,N-cyclopentamethylenethiocarbamyl-N′,N′-cyclopentamethylenesulfenamide (Part I, Ref. 1):



III is known to be a salt and should exhibit relatively high conductivity in a solvent of high dielectric constant. On the other hand, the sulfenamide is entirely covalent and its lack of ionization would contribute little to the conductivity of the solution. The conductivity of II or II-alternate should be near that of either III or the sulfenamide. Specific conductances of 0.01 M solutions in ohm^{-1} cm.$^{-1}$ at 25° were:

Nitrobenzene	5.5×10^{-9}
Sulfenamide (covalent)	5.5×10^{-9}
III (electrovalent)	18.0×10^{-9}
II or II-alternate	6.6×10^{-9}

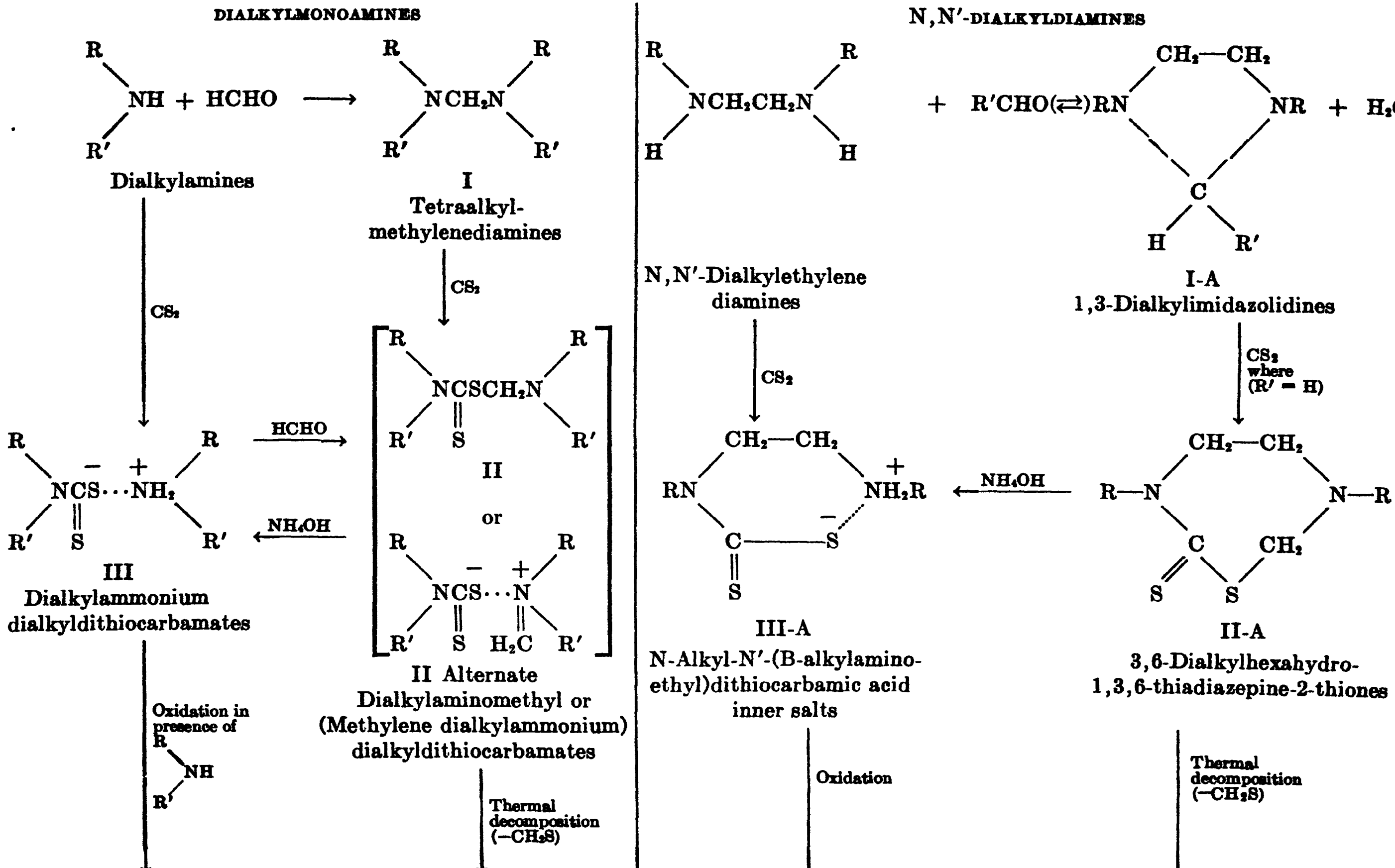
Thus, the similarity of II and the covalent sulfenamide conductivities supports the covalent ester structure, II, rather than the electrovalent structure, II-alternate, proposed by Levi. Further evidence for II rather than II-alternate is based on the high solubilities in benzene and ether and the low melting points exhibited by this type of compound, for in this respect they also resemble the covalent sulfenamide. However, the corresponding salts (III) from which they may be derived show, as would be predicted, low solubilities in these solvents and high melting points.

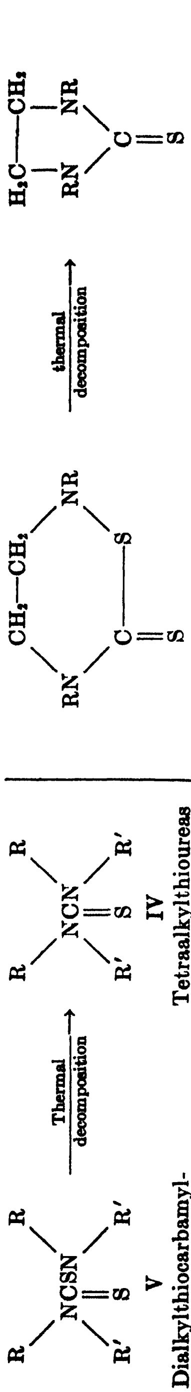
Fisher-Hirschfelder-Taylor models show that the suggested aminomethylene thioester structure is arranged in such a way that, for normal bond angles the sulfur and nitrogen atoms are forced close together,  perhaps close enough to interact and to produce a strain sufficiently large to explain the ease of splitting of the molecule by aqueous alkali (including ammonia), to produce

[2] These conductivities in nitrobenzene were determined by Mr. P. H. Biddison of this laboratory.

CHART I

SUMMARY OF AMINE-ALDEHYDE-CARBON DISULFIDE REACTIONS





V
Dialkylthiocarbamylsulfenamides

IV
Tetraalkylthioureas

V-A
2,5-Dialkyltetrahydro-1,2,5-thiadiazine-6-thiones

IV-A
1,3-Dialkyl-2-imidazolidinethiones

dithiocarbamate salts. This reaction was noted by Levi and was confirmed by us for both open chain and heterocyclic compounds.

Whereas the dialkylamine-formaldehyde condensation forms methylenediamines (I), reactions of N,N′-dialkylethylenediamines with aldehydes result in the formation of the heterocyclic imidazolidine ring (I-A). The preparation and properties of 1,3-diaryl- and 1,3-diaralkyl-imidazolidines have been studied

TABLE I

PROPERTIES OF 1,3-DIALKYLIMIDAZOLIDINES (I-A)

R IN IMIDAZOLIDINE FORMULA (I-A)	R′	YIELD,[a] %	DISTILLATION RANGE, °C./MM.	n^{25}_D	d^{25}_4	ANALYSES, N Calc'd	Found[b]
Ethyl	H	65	65.5/35	—	0.858	21.86	21.60
Ethyl	Propyl	85.5	68–73/10	1.4473	.845	16.45	16.20
Ethyl	Phenyl	60.5	94/2.5	1.5128	.945	13.71	13.79
Allyl	H	64	73–74.5/10	1.4708	.887	18.40	18.20
Allyl	Propyl	80.5	96–97/10	1.4666	.868	14.40	14.43
Allyl	Phenyl	75	114/2.5	1.5265	.957	12.26	12.25
Isopropyl	H	73.5	67/10	1.4479	.851	17.92	18.10
Isopropyl	Propyl	81	91.5–93/10	1.4520	.856	14.12	14.03
Isopropyl	Phenyl	69	114/2.5	1.5111	.947	12.05	12.00
n-Butyl	H	81.5	105–106/10	1.4497	.846	15.19	15.20
n-Butyl	Propyl	87.5	121–125/10	1.4511	.842	12.37	12.15
n-Butyl	Phenyl	86	110–111/0.7	1.5001	.919	10.75	10.75
1-Methylbutyl	H	81	120.5/10	1.4570	.857	13.19	13.28
1-Methylbutyl	Propyl	85.5	103–107/2.5	1.4540	.849	11.01	11.10
1-Methylbutyl	Phenyl	90	116–118/0.7	1.4987	.916	9.68	9.71
Cyclohexyl	H	79	146/2.5	1.5049	.973	11.85	11.80
Cyclohexyl	Propyl	67.5	135–137/0.7	1.5005	.958	10.06	10.16
Cyclohexyl	Phenyl	67.5	m.p. 59.2–59.6 (corr.)	—	—	8.96	8.95
Phenyl	H	66	m.p. 124.6–124.8[c]	—	—	12.49	12.47
Phenyl	Propyl	37.5	m.p. 80.0–80.8 (corr.)	—	—	10.51	10.48
Phenyl	Phenyl	82.5	m.p. 136.4–136.8[d] (corr.)	—	—	9.32	9.25
2-Ethylhexyl	H	90.5	132/0.7	1.4588	.818	9.42	9.35
2-Ethylhexyl	Propyl	87	158–159/0.7	1.4594	.844	8.27	8.31
2-Ethylhexyl	Phenyl	81.5	164/0.7	1.4908	.893	7.51	7.60

[a] The yield was determined of purified compound calculated to 0.5% and based on diamine reactant. [b] The nitrogen analyses were carried out by the micro-Friedrich-Kjeldahl method. [c] Bischoff (10) reported 124°. [d] Moos (9) reported 137°.

by van Alphen (6) Lob (7), Rameau (8), Moos (9), Bischoff (10), and Scholtz and Jaroff (11). However, 1,3-dialkylimidazolidines have not been reported in the literature. Consequently, a compilation of properties of those prepared for this investigation is presented in Table I. Their synthesis was achieved by the condensation of each of three aldehydes: formaldehyde, butyraldehyde, and benzaldehyde with N,N′-disubstituted ethylenediamines in which the substitutents were ethyl, allyl, isopropyl, *n*-butyl, 1-methylbutyl, cyclohexyl, phenyl, and 2-ethylhexyl. This condensation proceeded most readily with formaldehyde,

with or without a solvent, giving a good yield of the corresponding 1,3-imidazolidine. With butyraldehyde and benzaldehyde, the reactions producing 2-substitured imidazolidines proceeded more slowly, and were aided by warming in the presence of toluene and separation of the water formed.

1,3-Dialkylimidazolidines and carbon disulfide reacted at room temperature in ether or alcohol. The product which precipitated on cooling the reaction mixture was a fairly pure, yellow crystalline material with no odor. Analyses for sulfur and nitrogen corresponded to a reaction between equimolar quantities of each reactant. An interpretation of the imidazolidine-carbon disulfide reaction is facilitated by considering an imidazolidine as a methylenediamine in which the nitrogen atoms are linked by an ethylene chain. Thus, the formation of a 3,6-dialkylhexahydro-1,3,6-thiadiazepine-2-thione (II-A) has been postulated as the diamine analog of II. Fisher-Hirschfelder-Taylor models of these compounds show that the ring atoms form a strain-free seven-membered ring. This model,

TABLE II

3,6-DIALKYLHEXAHYDRO-1,3,6-THIADIAZEPINE-2-THIONES (II-A)

R IN THIADIAZEPINE FORMULA (II-A)	REACTION SOLVENT	YIELD, %	M.P., °C. (CORR.)	ANALYSES			
				Calc'd		Found	
				N	S	N[a]	S[b]
Ethyl	ether	86	68.4–69.4	13.72	31.40	13.82	31.52
Isopropyl	alcohol	82	103.0	12.07	27.58	12.05	27.20
n-Butyl	ether	61	61.4–61.8	10.78	24.59	10.75	24.55
Cyclohexyl	alcohol	97	98 –99.4	8.97	20.51	8.94	20.20

[a] The nitrogen analyses were carried out by the micro-Friedrich-Kjeldahl method.
[b] The sulfur analyses were made with a semi-micro Parr bomb.

however, lacks the symmetry and stability of the five-membered imidazolidine rings which may explain in part the observed decomposition of the former to the latter. The properties of four thiadiazepines are presented in Table II. An attempt to react 1,3-diphenylimidazolidine with carbon disulfide gave no evidence of reaction.

A different type of reaction was noted when the 2-position of the imidazolidine ring contained an alkyl (propyl) or aryl (phenyl) substituent. The product which separated from the mixture was not a thiadiazepine derivative, but an N-alkyl-N-(β-alkylaminoethyl)dithiocarbamic acid inner salt (III-A). The latter was also the product of a dialkylethylenediamine-carbon disulfide reaction (Part I).

The failure to form the expected thiadiazepines from the 2-substituted imidazolidines may be related to the sluggishness with which these imidazolidines were formed. If the reaction of aldehyde with diamine to form imidazolidine and water is reversible, which is likely, it is indicated that the reverse reaction, or hydrolysis, took place much more readily with the 2-substituted imidazolidines. It would then be concluded that, in reacting the 2-substituted imidazolidines

with carbon disulfide in alcohol, hydrolysis first took place to form the original dialkylethylenediamines, which then reacted with the carbon disulfide to form the highly insoluble inner salts of the N-alkyl-N-(β-alkylaminoethyl)dithiocarbamic acids (III-A).

An imidazolidine-2-thione(IV-A) was identified as the thermal-decomposition product of a hexahydro-1,3,6-thiadiazepine-2-thione. Similar degradation to the 5-membered ring was shown in Part I to occur in the decomposition of the N-alkyl-N-(β-alkylaminoethyl)dithiocarbamic acids (III-A), and their oxidation products, the 2,5-dialkyltetrahydro-1,2,5-thiadiazine-6-thiones (V-A). The odor which the thiadiazepine compounds developed on standing indicated the instability of the compounds and suggests that the imidazolidine-2-thione was formed by loss of thioformaldehyde from the ring. The decomposition appears to be greatly accelerated by traces of impurity in the product. The parallel thermal decomposition of the dialkylaminomethyl dithiocarbamate esters (II or II-A) to form thioureas has not been reported. Preliminary experiments in this laboratory here yielded complex reaction mixtures which have not been investigated further.

Levi reported that his dialkylammonium dithiocarbamate-formaldehyde products (II-alternate) on treatment with heavy-metal salt solutions precipitated the metal dithiocarbamates. Likewise, he reported their oxidation to thiuram disulfides. These observations of Levi were confirmed, and in addition, dilute ammonia water or an aqueous solution of a volatile amine with II was shown to effect removal of the methylene group leaving the original dialkylammonium salt of the dialkyldithiocarbamic acid (III).

In the diamine series, the hexahydro-1,3,6-thiadiazepine-2-thiones dissolved almost completely in dilute aqueous ammonia. Following volatilization of ammonia on standing in an open dish for a few hours, white crystalline solids precipitated in the water. These products were identified as the inner salts of N-alkyl-N-(β-alkylaminoethyl)dithiocarbamic acids (III-A). This easy hydrolytic splitting of the thiadiazepine ring with elimination of formaldehyde and the formation of a six-membered ring with an electrovalent linkage is exactly analogous to the splitting of the aminomethylene dithiocarbamate esters by aqueous alkali or ammonia to form the dithiocarbamate salts.

In carrying out the oxidation of the aminomethylene dithiocarbamate esters (II or II-alternate) and also of the thiadiazepines (II-A), these compounds were invariably first dissolved in dilute aqueous alkali. Hence the solution undoubtedly did not contain the unchanged starting materials, but contained dithiocarbamate salts instead. It is, therefore, not surprising that subsequent oxidation of the aqueous solutions produced thiuram disulfides (I) in the first case, and the 2,5-dialkyl tetrahydro-1,2,5-thiadiazine-6-thiones (V-A) from the cyclic dithiocarbamate inner salt intermediates (III-A) in the second case.

EXPERIMENTAL

Preparation of N′,N′-cyclopentamethyleneaminomethyl N,N-cyclopentamethylenedithiocarbamate (Dithioester II or Salt II-alternate) by three methods. Method 1 (1). The reaction

between 0.20 mole of methylene-*bis*-piperidine and 0.20 mole of carbon disulfide was performed in 200 cc. of alcohol at 5–10°. The white solid which separated was filtered and recrystallized from alcohol, m.p. 59.0–59.5° (corr.).

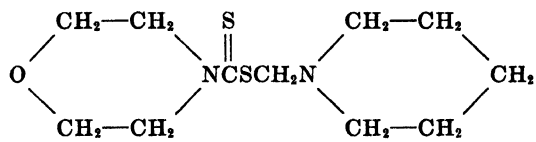
Method 2. (4). One-half mole of piperidinium N,N-cyclopentamethylenedithiocarbamate suspended in 200 cc. of alcohol was treated with 0.55 mole of formaldehyde (as 35–40% formalin). The slurry appeared partially to dissolve and after 12 hours at 0°, the white precipitate was filtered, m.p. 58.9–59.4°. Mixture m.p. with preparation of Method 1 was 58.8–59.4°, thereby establishing identity.

With each of these methods similar results were observed when the R and R′ groups were ethyl or oxadiethylene (from morpholine).

Method 3. Piperidinomethanol was prepared by slowly adding 0.5 mole of piperidine to 0.5 mole of formaldehyde (as 35–40% formalin). The temperature was kept below 15° by external cooling. This aqueous solution of piperidinomethanol was added slowly to a mixture of 0.32 mole (40 g.) of piperidinium N,N-cyclopentamethylenedithiocarbamate suspended in 250 cc. of alcohol. The slurry appeared to dissolve partially, but on cooling to 5°, it became pasty. The white product was recrystallized from alcohol, m.p. 58.6–59.2°; a mixture m.p. with the product from Method 1 was 58.8–59.4°.

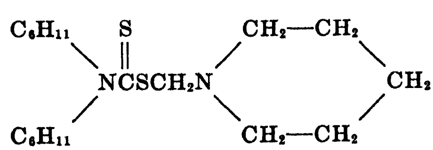
This reaction also was applied successfully to two other dithiocarbamates;

(*a*) An aqueous solution containing 0.1 mole of piperidinomethanol was added to a slurry of 0.067 mole (16.7 g.) of morpholinium N,N-oxadiethylenedithiocarbamate in 100 cc. of alcohol. After a few minutes the salt partially dissolved, insoluble matter was filtered, and the filtrate was placed in a refrigerator. After standing, crystalline plates were obtained, m.p. 88–90.5° (corr.), after recrystallization from ether-acetone. The product is assumed to have the structure:



Anal. Calc'd for $C_{11}H_{20}N_2OS_2$: N, 10.76; S, 24.62.
Found: N, 10.50; S, 24.75.

(*b*) An aqueous solution containing 0.1 mole of piperidinomethanol was added to 0.059 mole (25.7 g.) of dicyclohexylammonium dicyclohexyldithiocarbamate suspended in 75 cc. of alcohol. After a little agitation the slurry dissolved. The solution was poured into water whereupon a yellow oil separated. This oil crystallized on cooling. After washing with ether, the product melted at 114.5–116° (corr.). The structure is presumably:



Anal. Calc'd for $C_{19}H_{34}N_2S_2$: N, 7.90; S, 18.08.
Found: N, 7.42; S, 18.35.

Reaction of N′,N′-dialkylaminoethyl N,N-dialkyldithiocarbamates (II or II-alternate) with amines. A small quantity of each of the above dithioesters II (II-A) was suspended in water and sufficient amine (ammonia, ethylamine, etc.) added to dissolve the material. The solutions were allowed to stand in a watch glass exposed to air. White crystals precipitated during evaporation of the solvent. They were identified as the corresponding amine salt of the dithiocarbamic acid (III) by mixture melting point determinations with authentic samples.

Oxidation of II (or II-alternate) to thiuram disulfides. A dilute alkali solution of each of the above dithioesters II (or salt II-alternate) was oxidized with iodine-potassium iodide at

room temperature. The precipitated oxidation products were identified as thiuram disulfides by mixture melting point determinations with authentic samples.

Preparation of imidazolidines (I-A). In addition to the diamines described in Part I, several additional N,N′-dialkyl- and N,N′-diphenyl-ethylenediamines were used for the preparation of imidazolidines. They were prepared in the usual manner from the monoamine and ethylene dichloride. N,N′-diallylethylenediamine is a colorless liquid, b.p. 67.5–70°/6 N,N′-diphenylethylenediamine distilled at 178–182°/2 and solidified in the receiver on cooling.

1,3-Disubstituted imidazolidines were prepared by slowly adding formaldehyde (as 35–40% formalin) in 10% molar excess to the diamine. A highly exothermic reaction ensued and the addition of formalin was regulated to keep the temperature below 50°. When diethyl-, diisopropyl-, and dicyclohexyl-ethylenediamines were used, formation of the diamine hydrate on addition of formalin caused solidification of the reaction mixture; on further addition of formalin, the mass liquidified. At the completion of most of the reactions, two liquid phases—water and imidazolidine—were present. Separation of the diethyl-, diallyl-, and diisopropyl-imidazolidines was induced by salting.

The 2-propyl- and 2-phenyl-dialkylimidazolidines were prepared in warm toluene (50–60°) solution from the diamine and butyraldehyde, or benzaldehyde. The diamines which contained the larger N-substituents such as phenyl or 2-ethylhexyl reacted somewhat sluggishly and these reaction mixtures were refluxed for one hour. The by-product water from each reaction was withdrawn and the toluene removed by distillation.

The liquid imidazolidines were purified by distillation through a six-inch Vigreux column. Yields shown in Table I are those of purified products. Solid products were recrystallized from benzene.

Preparation of 3,6-dialkylhexahydro-1,3,6-thiadiazepine-2-thiones (II-A). Solutions of 1,3-diethyl-, diisopropyl-, dibutyl-, and dicyclohexyl-imidazolidines (20%) in the solvent indicated in Table II were treated with a 10% molar excess of carbon disulfide, added at a sufficiently slow rate to permit dissipation of the heat of reaction. The solutions became yellow and were maintained at room temperature for two hours; then they were placed in the refrigerator overnight. An oily layer separated from the diethyl- and dibutyl-imidazolidine reaction mixtures; on cooling in a Dry Ice-acetone bath, the oils solidified to canary yellow crystals. Diisopropyl- and dicyclohexyl-imidazolidine-carbon disulfide products separated as solids and were recrystallized from slightly warm acetone; the ease of thermal decomposition necessitated caution in purification.

Thermal decomposition of 3,6-dialkylhexahydro-1,3,6-thiadiazepine-2-thiones (II-A) to 1,3-dialkylimidazolidine-2-thiones (IV-A). A few grams of each thiadiazepine (II-A) (Table II), dissolved in alcohol, was refluxed. The white solid (trithioformaldehyde?) which precipitated was filtered. The imidazolidine-2-thiones (IV-A) were crystallized from the alcoholic solution and identified by a mixture melting point with an authentic sample in each case.

The 1,2,3-trisubstitutedimidazolidine-carbon disulfide reaction. A solution of 9.8 g. of 1,3-dicyclohexyl-2-phenylimidazolidine in 30 cc. of alcohol was agitated while 2.5 g. of carbon disulfide were added slowly. A white solid began to precipitate almost immediately; after two hours it was filtered and washed with acetone, yield 8.9 g. The product decomposed at 166°; it was identified as N-cyclohexyl-N-(β-cyclohexylaminoethyl)dithiocarbamic acid inner salt (III-A, R = cyclohexyl):

Anal. Calc'd for $C_{15}H_{28}N_2S_2$: N, 9.33; S, 21.3.

Found: N, 9.41; S, 21.2.

This reaction was applied to other imidazolidines as follows: the 1,3-diethyl-2-propyl-, 1,3-diisopropyl-2-propyl-, and 1,3-dicyclohexyl-2-propyl- imidazolidines also gave III-A as shown by the temperatures and manner of decomposition of the reaction products.

The 3,6-dialkylhexahydro-1,3,6-thiadiazepine-2-thione (II-A). *Reaction with ammonia.* A few grams of II-A (Table II) in dilute ammonia water was stirred to dissolve the compound and this was then filtered; usually a very small amount of insoluble matter was

present. The clear filtrate was placed in an evaporating dish for a few hours whereupon white crystals precipitated. They were identified as N-alkyl-N-(β-alkylaminoethyl)dithiocarbamic acids (III-A) by the temperature and nature of decomposition.

Oxidation of 3,6-dialkylhexahydro-1,3,6-thiadiazepine-2-thiones (II-A) to 2,5-dialkyltetrahydro-1,2,5-thiadiazine-6-thiones (V-A). A solution of 0.01 mole II-A (Table II) in 100 cc. of 0.1 *M* sodium hydroxide was stirred while aqueous iodine-potassium iodide solution was added dropwise. The oxidation product precipitated and after recrystallization was identified as the corresponding 2,5-dialkyltetrahydro-1,2,5-thiadiazine-6-thione (V-A) by mixture melting point determinations with authentic samples.

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SUMMARY

1. The reaction products of methylenediamines and carbon disulfide have been postulated as dithioesters, N′,N′-dialkylaminomethyl N,N-dialkyldithiocarbamates.

2. A series of new 1,3-dialkyl-, 1,3-dialkyl-2-propyl-, and 1,3-dialkyl-2-phenylimidazolidines was prepared.

3. The addition of carbon disulfide to 1,3-dialkylimidazolidines gave compounds to which have been assigned the structure of 3,6-dialkylhexahydro-1,3,6-thiadiazepine-2-thiones. Decomposition of the latter by loss of thioformaldehyde yielded 1,3-dialkylimidazolidine-2-thiones. With dilute ammonium hydroxide the thiadiazepines formed the inner salts of N-alkyl-N-(β-alkylaminoethyl)dithiocarbamic acids while halogens oxidized the aqueous solutions to 2,5-dialkyl-1,2,5-thiadiazine-6-thiones.

4. No reaction of 1,3-diphenylimidazolidine with carbon disulfide was evident.

5. If the 2-position on a 1,3-dialkylimidazolidine was substituted by an alkyl (propyl) or aryl (phenyl) group, the reaction with carbon disulfide formed the inner salt of an N-alkyl-N-(β-alkylaminoethyl)dithiocarbamic acid.

AKRON 17, OHIO

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[CONTRIBUTION FROM THE CHEMICAL AND PHYSICAL RESEARCH LABORATORIES OF THE FIRESTONE TIRE AND RUBBER COMPANY]

OXIDATIVE CONDENSATION REACTIONS OF AMINES WITH CARBIDITHIOATES AND XANTHATES[1]

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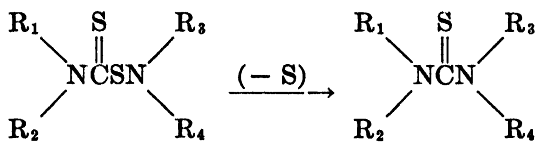
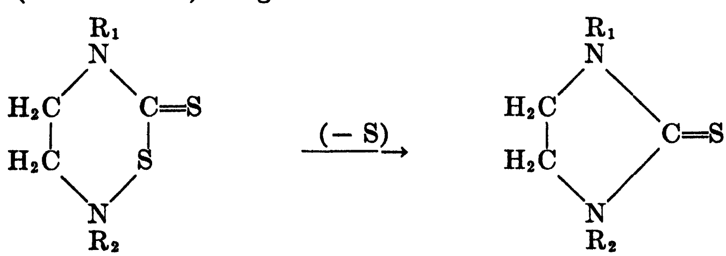
Thioamides or disulfides were found to be the products of the oxidative condensation of the sodium salts of carbidithioates and cyclohexylamine. These results contrast with those obtained by ourselves and others and discussed in the first paper of this series, that oxidative condensation of amines with mercaptothiazoles and thiazolines resulted in the formation of thiazole- and thiazoline-sulfenamides (1). Later it was discovered that the oxidation of dithiocarbamate-amine mixtures produced thiocarbamylsulfenamides (2) and this work was extended to the formation of cyclicsulfenamides (6-thiotetrahydro-1,2,5-thiadiazines) from the inner salts of N-alkyl-N-(β-alkylaminoethyl)dithiocarbamic acids (3). In the course of this earlier work it was discovered that the thiocarbamylsulfenamides more or less readily lost sulfur forming thioureas (2).

1. 

Similarly the tetrahydro-1,2,5-thiadiazines lost sulfur on heating, the cyclic thioureas (imidazolidines) being formed.

2. 

It is suggested that thioacylsulfenamides were the initial products of the oxidative condensation of sodium carbidithioates and cyclohexyl amine.

3. $$\mathrm{R\overset{\overset{S}{\|}}{C}SNa} + \mathrm{H_2NC_6H_{11}} \xrightarrow{(O)} \mathrm{R\overset{\overset{S}{\|}}{C}S\overset{H}{N}C_6H_{11}}$$

(R = aryl or furfuryl).

These thioacylsulfenamides were then unstable and decomposed immediately with loss of sulfur and the formation of thioamides.

[1] Presented before the Division of Organic Chemistry at the 114th meeting of the American Chemical Society, St. Louis, Mo., September, 1948.

$$4. \qquad R\overset{\overset{S}{\|}}{C}S\overset{H}{N}C_6H_{11} \xrightarrow{(-S)} R\overset{\overset{S}{\|}}{C}\overset{H}{N}C_6H_{11}$$

The use of chloroamines as intermediates in the synthesis of sulfenamides, which was successfully used for the preparation of thiocarbamyl- and thiazolesulfenamides (2), did not yield the expected sulfenamides from carbidithioates. The reaction of N-monochlorocyclohexylamine and sodium dithiofuroate yielded N-cyclohexylthiofuramide. Here also the sulfenamide was probably an intermediate product of the reaction.

Oxidation of a mixture of cyclohexylamine and sodium monothiobenzoate produced an oxygen amide.

$$5. \qquad C_6H_5COSNa + H_2NC_6H_{11} \xrightarrow{O} C_6H_5CONHC_6H_{11}$$

The benzoylsulfenamide was probably formed but lost sulfur immediately to form the amide.

$$6. \qquad C_6H_5COSNHR \xrightarrow{-S} C_6H_5CONHR$$

These thioamides are not reported in the literature and were identified in several cases by synthesis from the appropriate Grignard reagents and cyclohexyl isothiocyanate (4).

$$7. \qquad \begin{array}{l} RMgX + C_6H_{11}NCS \longrightarrow C_6H_{11}N\!=\!\underset{R}{C}SMgX \\ \qquad\qquad\qquad\qquad\qquad\quad \big\downarrow H_2O \\ \qquad\qquad\qquad MgX(OH) + C_6H_{11}\overset{H}{N}\overset{\overset{S}{\|}}{C}R \end{array}$$

It was shown by Debus (5) and Mylius (6) that ammonia reacted with xanthogen disulfides to form xanthogen amide and ammonium xanthogenate. We have found that cyclohexylamine reacted with xanthogen disulfides to form the N-cyclohexylxanthogenamide and the corresponding xanthogenate.

$$8. \quad RO\overset{\overset{S}{\|}}{C}SS\overset{\overset{S}{\|}}{C}OR + C_6H_{11}NH_2 \xrightarrow{(-S)} RO\overset{\overset{S}{\|}}{C}\overset{H}{N}C_6H_{11} + RO\overset{\overset{S}{\|}}{C}SNH_3C_6H_{11}$$

Oxidative condensation of xanthates with amines did not yield sulfenamides nor did the reaction of xanthates with N-monochloroamines. This was indicated by the fact that none of the products were accelerators of rubber vulcanization. Thioamides were not isolated but were probably the main constituents of the complex reaction mixtures.

Oxidative condensation of cyclohexylamine and sodium trithiocarbonate produced dicyclohexylthiourea. This also corresponds to the formation of thioamides from carbidithioates and probably involves initial formation of a *bis*-

sulfenamide with immediate decomposition by loss of sulfur and the formation of the thiourea.

$$9. \quad Na_2CS_3 + 2C_6H_{11}NH_2 \xrightarrow{(2\,O)} \begin{array}{c} S \\ \| \\ C_6H_{11}NHSCSNHC_6H_{11} \end{array} + 2\,NaOH$$

$$\downarrow (-2\,S)$$

$$\begin{array}{c} S \\ \| \\ C_6H_{11}NHCNHC_6H_{11} \end{array}$$

Disulfides were the products of a number of reactions designed to produce sulfenamides from carbidithioates and xanthates. The oxidation of cyclohexylammonium dithiofuroate yielded dithiofuroyl disulfide. N-Chlorourea and similar compounds did not react metathetically with sodium xanthates, but formed xanthogen disulfides.

EXPERIMENTAL

Preparation of dithio acids. Dithiobenzoic acid, α-dithionaphthoic acid, and dithio-*p*-toluic acid were prepared by reaction of the appropriate Grignard reagent and carbon disulfide as described by Houben and others (7). These acids were obtained in yields of 48%, 80%, and 30% respectively by this method.

α-Dithiofuroic acid was prepared by the action of sodium polysulfide on furfural according to the method of Leuck (8), which represents a modification of earlier work (9). Yields of 40–50% were obtained by us.

All of the dithio acids prepared were unstable, deep red or violet oils. They were purified by a series of extractions; that is, extraction of an ether solution of the acid with dilute aqueous alkali and extraction of the acidified aqueous solution of the sodium salt of the acid so formed with ether; this procedure was repeated until extraction of the ether solution by aqueous alkali left the ether layer colorless.

N-Cyclohexylthiobenzamide. To a solution of 13.2 g. (0.075 mole) of sodium dithiobenzoate in 250 ml. of water was added 37.5 g. (0.375 mole) of cyclohexylamine; to this a solution of 27 g. (0.1 mole) of iodine and 30 g. of potassium iodide in 200 ml. of water was added slowly and with stirring at a temperature of 5–10°. The red color of the solution disappeared and an oil formed. After allowing the reaction mixture to stand overnight, the oil was extracted with ether, the ether solution was washed several times with water and evaporated. The oily residue was triturated several times with water and gasoline added, after which the yellow crystalline solid was separated and dried. It melted at 82–85°. Recrystallized twice from gasoline, m.p. 91–92°.

Anal. Calc'd for $C_{13}H_{17}NS$: N, 6.40; S, 14.60.
Found: N, 6.44; S, 14.65.

This compound was also obtained from the reaction of sodium dithiobenzoate and N-monochlorocyclohexylamine, m.p. 90–92°; the mixture melting point 90–92°) with the above sample proved the two samples identical.

In order to establish definitely the structure of this compound, it was prepared by the reaction of phenylmagnesium bromide with cyclohexyl isothiocyanate.

To 0.08 mole of phenylmagnesium bromide in 200 ml. of ether was added 10.89 g. (0.077 mole) of cyclohexyl isothiocyanate in 50 ml. of ether. The reaction mixture was maintained below 5°, stirred, and the stirring continued at 5° for one hour after the addition was complete. The reaction mixture was allowed to come to room temperature, then poured on to ice, acidified, and the ether solution dried over sodium sulfate. Evaporation of the ether gave a solid residue, m.p. *ca.* 50°; yield, 15 g. (88%). Recrystallized once from gasoline,

m.p. 90–92°; mixture m.p. 90–92° (with material obtained from sodium dithiobenzoate as described above).

N-Cyclohexylthio-p-toluamide. This was prepared in a manner similar to that described above. After dissolving 0.3 mole of dithio-*p*-toluic acid, 2.9 g. of sodium hydroxide, and 15.7 g. (0.15 mole) of cyclohexylamine in water, the solution was diluted to 250 ml. and a solution of 8.09 g. (0.3 mole) of iodine dissolved in potassium iodide solution was added slowly and with stirring. The oily precipitate was isolated in ether, the ether solution dried, and evaporated. Yield, 6.7 g. of a pasty solid (95%) m.p. 80–90°. Repeated recrystallizations from ether-petroleum ether yielded a bright yellow crystalline compound, m.p. 104–105°.

Anal. Calc'd for $C_{14}H_{19}NS$: N, 6.00; S, 13.72.

Found: N, 5.96; S, 13.64.

N-Cyclohexylthio-α-naphthamide. To an aqueous solution of 100 g. (1.0 mole) of cyclohexylamine, 0.2 mole of sodium α-dithionaphthoate, and 4 g. of sodium hydroxide, was added at 5–10° with stirring, 0.2 moles of iodine (200 ml. of an iodine-potassium iodide solution 1.0 molar with respect to iodine). A bright yellow crystalline solid formed which turned to a red oil when the aqueous reaction medium was separated. The oil was triturated with several portions of water and finally with alcohol (95%); it solidified, m.p. 81–95°. Recrystallized repeatedly from ether, m.p. 97–98°.

Anal. Calc'd for $C_{17}H_{19}NS$: N, 5.19; S, 11.76.

Found: N, 5.19; S, 11.86.

To the Grignard reagent prepared from 23.4 g. (0.11 mole) of α-bromonaphthalene and 2.7 g. (0.11 mole) of magnesium in 200 ml. of ether was added slowly at 0–5°, 14.2 g. (0.1 mole) of cyclohexyl isothiocyanate dissolved in 50 ml. of ether. The temperature was maintained below 5° for two hours, with vigorous stirring. On allowing the mixture to stand over the weekend at room temperature a clear ether solution resulted. This was poured on to ice and the mixture was acidified. A solid which was insoluble in both water and ether separated, was removed, and the ether layer evaporated to an oil. This was dissolved in ether and from this solution on cooling to −10° separated a yellow crystalline solid which, after repeated recrystallizations, melted at 97–98°. Mixture melting point with the compound prepared from α-dithionaphthoic acid, was 96–98°, indicating identity.

N-Cyclohexylthiofuramide. A suspension of N-monochlorocyclohexylamine was prepared at −10° by adding 0.23 mole of sodium hypochlorite (86.8 ml., 2.65 *M*) to 0.25 mole of cyclohexylamine with stirring. To this suspension was added, also with stirring, a solution of 28.8 g. (0.2 mole) of dithiofuroic acid in 100 ml. of 10% sodium hydroxide solution. The solid precipitate was washed with water and dried ;yield 43 g. (quantitative). After several recrystallizations from petroleum ether the material melted at 81–82°.

Anal. Calc'd for $C_{11}H_{15}NOS$: N, 6.70; S, 15.3.

Found: N, 6.88; S, 15.3.

The oxidative condensation of cyclohexylamine with sodium thiobenzoate. Monothiobenzoic acid was prepared by the reaction of benzoyl chloride and freshly prepared potassium hydrosulfide. To 0.35 mole of sodium monothiobenzoate dissolved in 200 ml. of water was added 1.75 moles of cyclohexylamine and then 0.35 mole of iodine (350 ml., 1.0 *M* iodine-potassium iodide) was added slowly and with stirring at a temperature of 5–10°. The voluminous white precipitate was washed and dried; m.p. 146–147°. A mixture melting point with an authentic sample of *N-cyclohexylbenzamide* showed no depression.

Preparation of cyclohexylammonium dithiofuroate. To a solution of 25 g. (0.17 mole) of dithiofuroic acid in ether solution was added 16.8 g. (0.17 mole) of cyclohexylamine with stirring, the temperature being maintained at 0°. The cyclohexylammonium salt separated as deep red crystals. These were washed with ether and dried; yield 41 g. (quantitative), m.p. 110–112° with decomposition. After one recrystallization from water, m.p. 113–114° with decomposition.

Oxidation of cyclohexylammonium dithiofuroate with potassium ferricyanide. Cyclohexylammonium dithiofuroate (12.15 g., 0.05 mole) was suspended in 750 ml. of water and a solution of 32.9 g. (0.1 mole) of potassium ferricyanide in 200 ml. of water was added with stirring

at room temperature. The solution became colorless and a bright red precipitate formed. This was dried, m.p. 94–95°; yield 17 g., 92%. After one recrystallization from hexane, m.p. 100–101°. A mixture melting point with a known sample of dithiofuroyl disulfide showed no depression.

The oxidation of an aqueous solution of cyclohexylamine and sodium trithiocarbonate. A solution of sodium trithiocarbonate was prepared as described by Weeldenburg (10) from 22.8 g. of carbon disulfide, 33.6 g. of potassium hydroxide, and 200 ml. of water with the aid of a small amount of an emulsifying agent. Assuming that the reaction proceeds according to the equation,

10. $$3\ CS_2 + 6NaOH \rightarrow 2Na_2CS_3 + Na_2CO_3 + 3\ H_2O$$

the solution contained 0.2 mole of sodium trithiocarbonate. To half of this solution was added first, 24.4 g. of cyclohexylamine, and then a solution of 24.7 g. of iodine in 250 ml. of potassium iodide solution slowly and with stirring. Meanwhile the reaction mixture was cooled with ice-water. An oil separated which after standing overnight solidified to a mixture of red and cream-colored crystals. These were washed with water and dried. Yield, 12.4 g., m.p. 170–175°. After recrystallization from alcohol-water the m.p. was 175–177°. A mixture melting point with dicyclohexylthiourea prepared according to the method of Skita and Rolfe (11), m.p. 176–178°, showed no depression.

The reaction of cyclohexylamine with diethylxanthogen disulfide. Ten grams of diethylxanthogen disulfide was dissolved in 50 ml. of ether and into this was dropped slowly with stirring an ether solution containing 8.2 g. of cyclohexylamine. Reaction was almost immediate. A light yellow precipitate formed and there was some heat developed by the reaction. The rate of addition was maintained at such a slow rate that the temperature did not rise more than a few degrees. The precipitate was removed by filtration and was water-soluble (cyclohexylammonium ethylxanthate). The ether filtrate was evaporated leaving an oily mass of crystals; after recrystallization from petroleum ether three times, m.p. 49–50°.

Anal. Calc'd for $C_9H_{17}NOS$: N, 7.5. Found: N, 7.4.

The reaction of N-monochlorourea and potassium isopropylxanthate. A solution of 0.1 mole of N-monochlorourea was prepared by adding 63.9 ml. of a 1.57 molar solution of sodium hypochlorite to 6.05 g. (0.1 mole) of urea dissolved in 50 ml. of water at a temperature of 0–5°. To this solution was then added slowly and with stirring a solution of 17.4 g. (0.1 mole) of sodium isopropylxanthate dissolved in 50 ml. of water. The solid precipitate which formed was filtered off and dried, m.p. 55–57°. Diisopropylxanthogen disulfide has m.p. 58.5° (12).

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[Contribution from the Department of Chemistry and Chemical Engineering of the University of Pennsylvania]

THE SO-CALLED ACYLANTHRANILS (3,1,4-BENZOXAZONES). I. PREPARATION; REACTIONS WITH WATER, AMMONIA, AND ANILINE; STRUCTURE[1]

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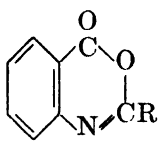
The class of compounds designated as acylanthranils,[3] or better 3,1,4-benzoxazones, has been represented hitherto by only 2-methylbenzoxazone (acetanthranil) and 2-phenylbenzoxazone (benzanthranil) and a number of derivatives of these with substituents mostly in the aromatic ring (1–12). The structure of the heteroelementary ring has not been decisively proved, some of the evidence being ambiguous (6, 13, 14, 15). A preference for the benzoxazone structure I is based partly on the improbability of the lactam structure II and of the *o*-quinonoid structure IIa, which last also seems inconsistent with the character of the acylanthranils. In the study reported herein there was developed a convenient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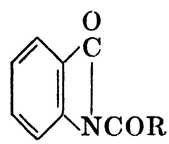
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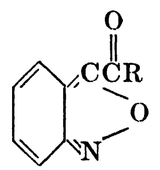
IIa

and fairly general procedure for preparation of 3,1,4-benzoxazones, of which eight new examples were obtained and characterized. Their chemical behaviors in several directions have been systematically examined, and new evidence as to structure is discussed.

Preparation of acylanthranils or 3,1,4-benzoxazones. The first representative of the class was made (16) by action of benzoyl chloride on anthranil, a method considered not suitable for extension owing to the instability of anthranil and the lack of a satisfactory method of preparation.[4] Bogert and Seil (5, 6) prepared acetanthranils by heating anthranilic acid or ring-substituted anthranilic acids with acetic anhydride, and by heating preformed N-acetyl- or N-benzoyl-an-

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[3] The acylanthranil names suggest methods of preparation from anthranil or anthranilic acid but their structural implications are deceptive. *Chemical Abstracts* treats these compounds as derivatives of 3,1,4-benzoxazone (Ring Index No. 947: 3,1,4H-benzoxazone), and for the most part they will be so named, sometimes in abbreviated form, in this paper. Grateful acknowledgement is made to Austin M. Patterson and Leonard T. Capell for advice as to nomenclature.

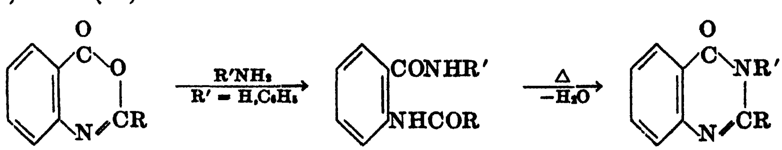
[4] Over-all yields of anthranil from *o*-nitrotoluene *via* *o*-nitrobenzaldehyde diacetate [Tsang, Wood, and Johnson, *Org. Syntheses*, **24**, 75 (1944); Vanino, *Praparative Chemie*, F. Enke, Stuttgart, 2nd Ed., Vol. II, 1923, p. 730] have barely exceeded 10%.

thranilic acids with acetic anhydride they obtained the corresponding acetanthranils and benzanthranils. Analogous procedures failed to yield 2-ethylbenzoxazones (propionanthranils) of demonstrated authenticity. The second procedure, judged to be the most promising of those available, was selected for study. Its usefulness depends upon whether or not acetic anhydride in general effects ring closure with acylanthranilic acids, and upon the extent to which acetic anhydride causes transacylation, leading to formation of acetanthranil, replacing wholly or in part the desired acylanthranil.

In the preparative procedure developed the acylanthranilic acid (Table VI) is heated with excess acetic anhydride, with slow distillation of the acetic acid formed in the reaction; after removal of excess acetic anhydride under reduced pressure the benzoxazone is isolated from the residue. In this way there were made the eleven benzoxazones listed in Table I. The method failed when R (formula I) was isobutyl, *n*-amyl, undecyl, and 3,5-dinitrobenzoyl. The optimum quantity of acetic anhydride was not determined in each case, but in the preparation of 2-methylbenzoxazone best results were obtained with about eight equivalents. The use of 90–95% ("practical") acetic anhydride instead of 99–100%, decreased yields only about 5%, but for difficult ring-closures it is probably necessary, and in general therefore advisable, to use acetic anhydride of high purity. Good yields of 2-ethylbenzoxazone and 2-*n*-propylbenzoxazone were obtained from anthranilic acid by interaction with propionic and *n*-butyric anhydrides, but the wider applicability of this method was not tested. Ring closure failed to occur when methyl anthranilate (instead of the acid) was heated with acetic anhydride. The product was N-acetylanthranilic ester or N,N-diacetylanthranilic ester, depending upon the severity of the treatment, but no 2-methylbenzoxazone was found.

Some reactions of 3,1,4-benzoxazones. Water. Bogert (12) reported the susceptibility of acetanthranil to hydrolysis; the initial cleavage to N-acetylanthranilic acid recalls that of benzoxazoles to acylaminophenols (18). This is a general characteristic of the benzoxazones, but their sensitivities to hydrolysis vary greatly. Formanthranil (3,1,4-benzoxazone) and acetanthranil (2-methyl-3,1,4-benzoxazone) are very sensitive, suffering deterioration due to atmospheric moisture[5] or to unsuspected moisture present in solvents. It appears that high 2-alkylbenzoxazones are increasingly stable toward hydrolysis, and that 2-arylbenzoxazones may be handled with no special precautions.

Ammonia and aniline. Stepwise conversion of acetanthranil and benzanthranil to substituted quinazolines (IV), *via* the *o*-acylaminobenzamides (III), by action of ammonia or primary amine was observed by Anschütz, *et al.* (19) and by Bogert, *et al.* (12):



I III IV

[5] Formanthranil is inherently unstable, and deteriorates under anhydrous conditions.

TABLE I

PREPARATION OF 3,1,4-BENZOXAZONES (ACYLANTHRANILS) BY ACTION OF ACETIC ANHYDRIDE ON N-ACYLANTHRANILIC ACIDS

3,1,4-BENZOXAZONE FORMULA I	MADE FROM[g]	YIELD[a], %	M.P., °C.	ANALYSIS	C	H	N
*3,1,4-Benzoxazone XIX (Formanthranil) R = H	V	56.8	43–44.4	Calc'd Found	65.3 65.2	3.43 3.53	9.53 9.62
2-Methyl- XX (Acetanthranil)	[b]	66.7	80–81[c]				
*2-Ethyl- XXI (Propionanthranil)	VI	74.7	85–86	Calc'd Found	68.5 68.5	5.18 5.10	8.00 8.09
*2-*n*-Propyl- XXII	VII	25.6	59–60	Calc'd Found	69.8 69.8	5.86 5.77	
2-Phenyl- XXIII (Benzanthranil)	X	81.0	123–124[d]				
*2-*o*-Tolyl- XXIV	XI	74.6	115	Calc'd Found	75.9 75.7	4.67 4.49	
*2-*p*-Tolyl- XXV	XII	58.5	154.5	Calc'd Found	75.9 75.7	4.67 4.48	
*2-*o*-Chlorophenyl- XXVI	XIII	91.0	139–140	Calc'd Found	65.3 65.1	3.13 3.07	
*2-*p*-Chlorophenyl- XXVII	XIV	89.4	190	Calc'd Found	65.3 65.2	3.13 3.03	
2-*o*-Nitrophenyl- XXVIII	XV	94.6	195–195.5[e]	Calc'd Found	62.7 62.5	3.01 3.14	
2-*p*-Nitrophenyl- XXIX	XVI	71.7	203[f]	Calc'd Found	62.7 62.6	3.01 2.88	
*2-(3-Pyridyl)- XXX	XVIII	80.8	153	Calc'd Found	69.7 69.8	3.60 3.43	

* Compound not reported previously.

[a] Yields of pure products.[b] Made from anthranilic acid.[c] Lit. m.p. 81–82° (5).[d] Lit m.p. 124.5° (12).[e] Lit. m.p. 197° (10).[f] Lit. m.p. 207° (12).[g] See Table VI.

These reactions were extended successfully to most of the benzoxazones available (Table I); the behaviors previously recorded, and those observed in the present study, permit the following conclusions.

Ammonia converts 3,1,4-benzoxazone and 2-methyl-3,1,4-benzoxazone, and presumably other 2-alkylbenzoxazones, to corresponding *o*-acylaminobenzamides (III) as isolable products when reaction occurs at or below room tempera-

ture, but moderate heating causes ring closure to IV. Conversion of benzanthranil and other 2-arylbenzoxazones to *o*-acylaminobenzamides (III; R = Ar; R′ = H) by action of ammonia requires moderate heating, and ring closure requires heating the dry amides above their melting points (20). The presence of an *ortho*

TABLE II

o-ACYLAMINOBENZAMIDES FROM 3,1,4-BENZOXAZONES BY ACTION OF AMMONIA

COMPOUND NO.	(FORMULA III; R′ = H) NAME	MADE FROM[f]	YIELD[a], %	M.P., °C.	ANALYSIS		
						C	H
XXXI	*o*-Formylaminobenzamide	XIX	33.1[b]	119–122[c]			
XXXII	*o*-Propionylaminobenzamide	XXI	[d]				
XXXIII	*o*-Butyrylaminobenzamide	XXII	[e]				
XXXIV	**o*-Toluylaminobenzamide	XXIV	24.4	217–218	Calc'd Found	70.8 71.0	5.55 5.21
XXXV	**p*-Toluylaminobenzamide	XXV	39.7	204–205	Calc'd Found	70.8 70.7	5.55 5.68
XXXVI	**o*-Chlorobenzoylaminobenzamide	XXVI	58.8	198–199	Calc'd Found	61.2 61.5	4.04 4.08
XXXVII	**p*-Chlorobenzoylaminobenzamide	XXVII	44.8	200.5	Calc'd Found	61.2 61.1	4.04 4.19
XXXVIII	**o*-Nitrobenzoylaminobenzamide	XXVIII	53.0	195	Calc d Found	58.9 59.0	3.89 3.94
XXXIX	**p*-Nitrobenzoylaminobenzamide	XXIX	61.5	235–236	Calc'd Found	58.9 58.9	3.89 3.77
XL	*Nicotinylaminobenzamide	XXX	53.9	211	Calc'd Found	64.7 64.7	4.60 4.43

* Compound not previously reported.

[a] Yields of pure products. [b] Reaction at 0°. [c] Lit. m.p. 123° (38). [d] Product was quinazolone XLII (Table III). [e] Product was quinazolone XLIII (Table III). [f] See Table I.

substituent in R prevented the ring closure. The essential results of the reactions with ammonia appear in Tables II and III.

Aniline reacts with benzoxazones at 100° or below to yield acylaminobenzamides (III; R′ = phenyl), which are readily prepared in this way. When R (in III) is aliphatic, conversion to IV requires heating to about 250°, but when R is aromatic, ring closure to IV at such temperature in the cases tested required the presence of zinc chloride. The presence of an *ortho*-substituent in R prevented or obstructed ring closure. In the two cases tested it was found that conversion of I

to IV in one operation was effected by condensation of the 2-alkylbenzoxazones with aniline at 150°, *i.e.*, at a temperature much lower than is required to cyclize the isolated intermediate III. Results of the experiments on the ring closure are given in Table V.

Transacylation experiments. Transacylation of N-acylanthranilic acids by heating with acetic anhydride under preparative conditions was observed to occur only with N-(3,5-dinitrobenzoyl)anthranilic acid and N-isovalerylanthranilic acid; the product in each case was 2-methylbenzoxazone (acetanthranil). Methyl

TABLE III

4-QUINAZOLONES FROM *o*-ACYLAMINOBENZAMIDES OR BENZOXAZONES BY ACTION OF AMMONIA

NUMBER	4-QUINAZOLONE FORMULA IV (R' = H)	MADE FROM	YIELD[a], %	M.P., °C.	ANALYSIS		
						C	H
XLI	Quinazolone-4	XXXI	47.2	216–217[b]			
XLII	Ethylquinazolone-4	XXI	52.2	233[c]	Calc'd Found	68.9 68.8	5.79 5.55
XLIII	*n-Propylquinazolone-4	XXII	43.1	200–201	Calc'd Found	70.2 70.2	6.43 6.31
XLIV	*p-Tolylquinazolone-4	XXXV	38.1	241–242	Calc'd Found	76.3 76.2	5.12 5.25
XLV	*p-Chlorophenyl-quinazolone-4	XXXVII	67.4	306[d]	Calc'd Found	65.5 65.3	3.54 3.35
XLVI	*p-Nitrophenyl-quinazolone-4	XXXIX	68.3	351–352[d]	Calc'd Found	62.9 63.2	3.47 3.67
XLVII	*3-Pyridylquinazolone-4	XL	41.5	276	Calc'd Found	69.9 69.8	4.06 3.94

* Compound not previously reported.

[a] Yield of pure product. [b] Previously reported: m.p. 216.5° (38). [c] Previously reported: m.p. 234° (39). [d] Observed; not corrected.

N-formylanthranilate suffered transacylation under more severe conditions (200°). Since none of the three compounds named was convertible to the benzoxazone by the preparative procedure, it may be concluded that transacylation may become noticeable or pronounced when ring closure to the benzoxazone is retarded or obstructed. Temperature may be a factor, for on heating N-formylanthranilic acid with propionic anhydride (b.p. 169°; which is considerably above the temperature of the usual reaction mixture) transacylation occurred and 2-ethylbenzoxazone was formed.

Transacylation involving displacement of the formyl group was induced in N-formylanthranilic acid by heating with acetic anhydride in presence of anhydrous sodium acetate or of γ-picoline. Only the formyl group could be thus re-

placed; when N-butyrylanthranilic acid or N-benzoylanthranilic acid was heated with acetic anhydride in presence of sodium acetate or with propionic anhydride, there was no evidence of transacylation.

The "transacylation" of benzoxazones (*i.e.*, conversion to other benzoxazones by action of suitable acid anhydrides) was tested by heating formanthranil with

TABLE IV

o-ACYLAMINOBENZANILIDES FROM 3,1,4-BENZOXAZONES BY ACTION OF ANILINE

NUMBER	*o*-ACYLAMINOBENZANILIDE FORMULA III; R' = C_6H_5	MADE FROM	YIELD[a], %	M.P., °C.	ANALYSIS		
						C	H
XLVIII	*Propionaminobenz-anilide	XXI	37.7	164	Calc'd Found	71.6 71.7	6.01 5.82
XLIX	**n*-Butyraminobenz-anilide	XXII	58.4	151–152	Calc'd Found	72.3 72.1	6.43 6.61
L	Benzoylaminobenz-anilide	XXIII	74.4	216–218[b]			
LI	**o*-Toluylaminobenz-anilide	XXIV	39.9	194.5	Calc'd Found	76.3 76.5	5.49 5.33
LII	**p*-Toluylaminobenz-anilide	XXV	51.8	220–221	Calc'd Found	76.3 76.1	5.49 5.50
LIII	**o*-Chlorobenzoylamino-benzanilide	XXVI	55.4	214–215	Calc'd Found	68.5 68.3	4.31 4.32
LIV	**p*-Chlorobenzoylamino-benzanilide	XXVII	52.5	236–237	Calc'd Found	68.5 68.6	4.31 4.22
LV	**o*-Nitrobenzoylamino-benzanilide	XXVIII	39.9	197	Calc'd Found	66.5 66.3	4.21 4.37
LVI	**p*-Nitrobenzoylamino-benzanilide	XXIX	53.3	207–208	Calc'd Found	66.5 66.5	4.21 4.20
LVII	*Nicotinylaminobenz-anilide	XXX	61.8	248–249	Calc'd Found	71.9 71.7	4.78 4.37

* Compound not previously reported.
[a] Yield of pure product. [b] Previously reported: m.p. 218–219° (40).

excess acetic anhydride in presence of sodium acetate, and by heating formanthranil, acetanthranil, and benzanthranil with propionic anhydride. The results were negative.

It is concluded that, with the exception of N-acylanthranilic acids not convertible to benzoxazones, transacylation is not recognizably operative during the preparative procedure described later, *i.e.*, that ring closure, when it can occur, proceeds more rapidly than transacylation.

Evidence as to structure of acylanthranils. The *ultraviolet spectrum* of 2-methylbenzoxazone (acetanthranil) and, for comparison, the spectra of isatoic anhydride both in presence and absence of triethylamine (to induce rearrangement to the imidol structure which is essentially identical with the benzoxazone structure), and of N-acetylanthranilic acid, were determined and are shown simultaneously in Figure 1. The absorptions of acetanthranil and isatoic anhydride show sufficient similarity to suggest related structures. The absorptions of isatoic anhydride in neutral and in alkaline environments are identical, indicating either failure of triethylamine to cause sensible shift to the imidol form or failure of the imidol structure to cause absorption within the range of energy levels of the light employed. The absorption of N-acetylanthranilic acid shows no close similarity to that of either isatoic anhydride or acetanthranil.

TABLE V

3-PHENYL-4-KETOQUINAZOLINES FROM *o*-ACYLAMINOBENZANILIDES BY HEAT

NUMBER	3-PHENYLQUINAZOLONE FORMULA IV: R' = C_6H_5 R	MADE FROM	YIELD[a], %	M.P., °C.	ANALYSIS		
						C	H
LVIII	*2-Ethyl	XLVIII	43.8	125–125.5	Calc'd Found	76.8 76.9	5.64 5.52
LIX	*2-*n*-Propyl	XLIX	53.2	120–121	Calc'd Found	77.3 77.2	6.10 5.95
LX	2-Phenyl	L	41.9	156–157[b]			
LXI	*2-*o*-Tolyl	LI	16.1	179–180	Calc'd Found	80.7 80.6	5.16 5.20
LXII	*2-*p*-Tolyl	LII	54.6	178	Calc'd Found	80.7 80.8	5.16 5.06
LXIII	*2-*p*-Chlorophenyl	LIV	39.8	177	Calc'd Found	72.2 72.1	3.94 3.72
LXIV	*2-*p*-Nitrophenyl	LVI	43.2	224–225	Calc'd Found	70.0 70.1	3.82 3.64
LXV	*2-β-Pyridyl	LVII	57.7	175–176.5	Calc'd Found	76.2 76.1	4.38 4.36

* Compound not reported previously.
[a] Yield of pure product. [b] Previously reported: m.p. 158–159° (41).

The *infrared absorption spectrum* of acetanthranil is shown in Figure 2. No features capable of unequivocal interpretation in terms of structure are recognizable in absence of data for compounds of related structures. A broadening of the absorption of the carbonyl group in the 1700 cm^{-1} region may be attributable to the effects of other groupings which absorb frequencies somewhat lower or

TABLE VI

N-ACYLANTHRANILIC ACIDS

NUMBER	COMPOUND N-···ANTHRANILIC ACID	REFERENCE FOR PREP.	YIELD, %	M.P., °C.	ANALYSIS			
						C	H	N
V	Formyl	[a]	90	167[b]	Calc'd Found[c]	58.2 58.1	4.28 4.31	
VI	Propionyl	23	71.3	114–115[d]				
VII	*n-Butyryl	24	32.6	118–118.5	Calc'd Found	63.7 63.1	6.33 6.19	6.76 6.72
VIII	Isovaleryl	24	33.5	115–116[e]				
IX	n-Caproyl	24	32.8	99–103[f]				
	Lauryl	24	40.8	92	Calc'd Found	71.4 71.6	9.15 9.01	
X	Benzoyl	24	99.2	182–183[g]				
XI	*o-Toluyl	24, 26, 27	31.6	193–194	Calc'd Found	70.6 70.5	5.13 5.20	
XII	*p-Toluyl	24, 26, 27	82.5	193–194	Calc'd Found	70.6 70.5	5.13 5.24	
XIII	*o-Chlorobenzoyl	24, 27	59.6	186.5–187	Calc'd Found	61.0 60.5	3.66 3.48	
XIV	*p-Chlorobenzoyl	24, 27, 28	96.8	204–205	Calc'd Found	61.0 61.0	3.66 3.65	
XV	o-Nitrobenzoyl	24, 27	57.0	234–235[h]				
XVI	p-Nitrobenzoyl	24, 27	77.5	235.5[i]				
XVII	*3,5-Dinitrobenzoyl	24[k]	54.7	208–209 dec.	Calc'd[j] Found	48.1 48.4	3.17 3.03	
XVIII	*Nicotinyl	24, 29	71.0	263–264	Calc'd Found	64.5 64.5	4.16 4.25	

* Compounds not previously reported.

[a] Preparative method described in text. [b] Lit. m.p. 168° (25). [c] Meyer and Bellman (25) reported the compound to be a hemihydrate; C, 55.2; H, 4.53. Compound V is anhydrous. [d] Lit. m.p. 117° (42). [e] Lit. m.p. 114–115° (43). [f] Lit. m.p. 94–95° (17). [g] Lit. m.p. 182° (24). [h] Lit. m.p. 239° (10). [i] Lit. m.p. 235.5° (12). [j] Calculated as monohydrate; recrystallized from aqueous ethanol. [k] 3,5-Dinitrobenzoyl chloride dissolved in diethyl ether.

somewhat higher. The side ring of structure I consists of such groupings, *viz.*, —O—C═O (1720–1750 cm^{-1}) and —C═N— (1580–1660 cm^{-1}), and might

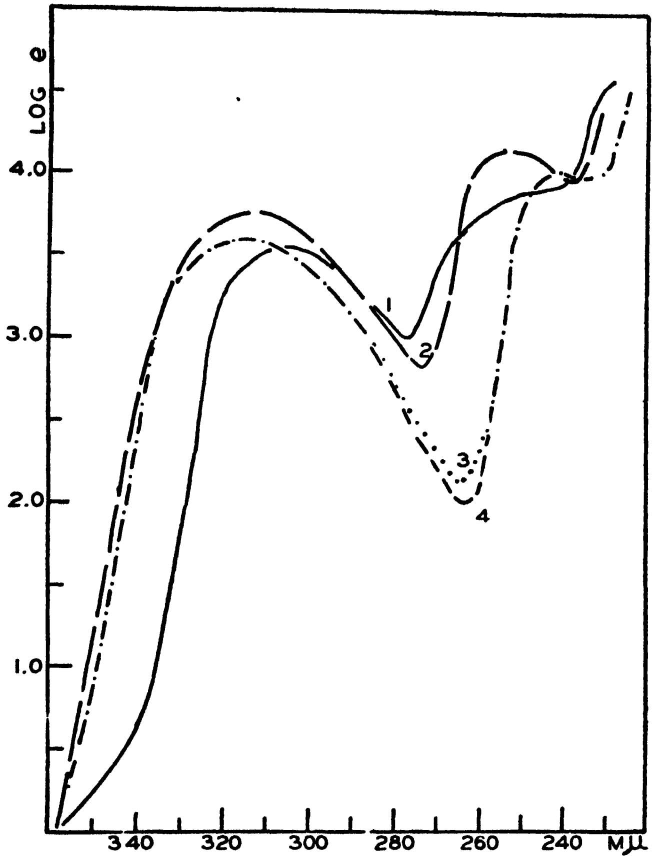


FIGURE 1. ULTRAVIOLET ABSORPTION SPECTRA: of Acetanthranil (Curve 1), N-Acetyl-anthranilic Acid (Curve 2), Isatoic Anhydride (Neutral dioxane) (Curve 3), and Isatoic Anhydride (Alkaline dioxane) (Curve 4).

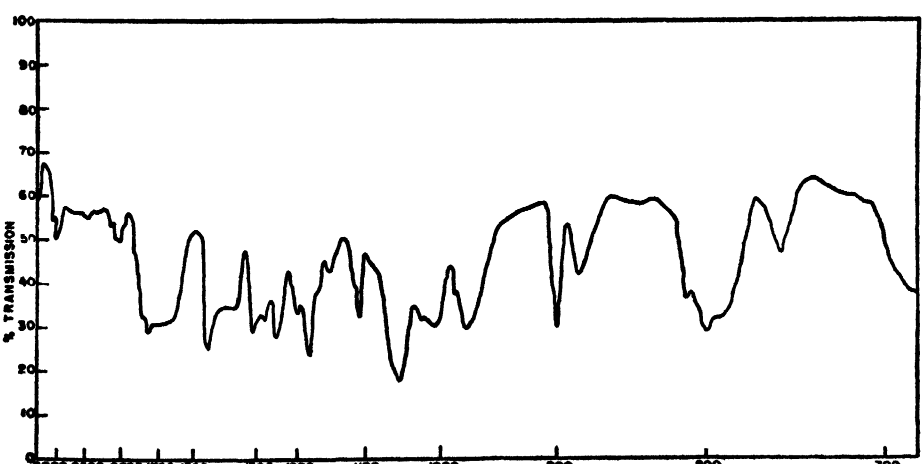


FIGURE 2. INFRARED ABSORPTION SPECTRUM OF ACETANTHRANIL

introduce the further effect of ring-strained carbonyl (1740–1800 cm^{-1}). As somewhat similar conclusions based on structures II or IIa can be reached, the interpretation of the infrared evidence is uncertain.

Certain of the chemical results permit inferences which support the belief that acylanthranils have the benzoxazone structure. 1. The failure to obtain acylanthranils from N-acylanthranilic acids in which R of the acyl group RCO contains a fairly long aliphatic chain (*n*-amyl, undecyl), or units which are obstructive sterically (isobutyl) or otherwise (3,5-dinitrobenzoyl), is more readily understandable if acylanthranils have the benzoxazone structure I than if the structure is II. In structure II it may be supposed that any interference of which the group R is capable will be diminished or absent because the carbonyl carbon separates R from the nitrogen atom involved in the ring closure. If the structure is I no such separation exists and any potentially restrictive character possessed by R will be operative in affecting the ease of ring closure. 2. The transacylation experiments yielded several results which show that structure II, against which the steric objections are strong but the chemical evidence is ambiguous, must be declared inadmissible on chemical grounds. The formyl group of N-formylanthranilic acid is replaced by either the acetyl or the propionyl group by heating with acetic anhydride in presence of sodium acetate or by heating with propionic anhydride; under the same conditions formanthranil is unchanged. If formanthranil has structure II, with the formyl group exposed in the same manner as in N-formylanthranilic acid, transacylation should occur as it does with N-formylanthranilic acid. The fact that formanthranil is unaffected justifies the conclusion that it contains *no formyl group attached to nitrogen* and that structure II is unacceptable. The stability of formanthranil towards acetic or propionic anhydride is entirely consistent with structure I, which could suffer "transacylation" only following ring rupture, which is unlikely, since the anhydride present in excess is actually an agent qualified to close the ring and since water, which opens the ring very readily, is necessarily absent.

It is believed that the foregoing arguments are sufficiently cogent to eliminate any residual doubt that the so-called acylanthranils are 3,1,4-benzoxazones of structure I.

EXPERIMENTAL

General. Melting and boiling points are corrected. Semimicro analyses for carbon and hydrogen (21, 22) and for nitrogen (23) were performed by Sarah M. Woods, of this laboratory.

N-Acylanthranilic acids were prepared by the method of Steiger (24), except that formylanthranilic acid was made as follows. A mixture of 68.5 g. (0.50 mole) of anthranilic acid in 500 ml. of benzene and 57 ml.)*ca.* 1.5 mole) of 99% formic acid was heated under reflux for three hours. The reaction mixture was chilled in ice, the caked solid was broken up, washed with benzene, and dried at 110°. The crude product (74.5 g., 90%) melted at 167°; recrystallization from ethyl acetate removed the color but did not change the m.p. The compound was water-free, and not the hemihydrate reported by Meyer and Bellman (25). Collected data for this and other acylanthranilic acids appear in Table VI.

Toluyl chlorides (*o*- and *p*-) were made from the nitriles (26) *via* the acids (27), of which *p*-chlorobenzoic acid was obtained by oxidation of *p*-chlorotoluene (28). Nitrobenzoyl

chlorides (*o*- and *p*-) were made from the acids (27) and nicotinyl chloride by the procedure of Berger, Alfriend, and Deinet (29).

Preparation of 3,1,4-benzoxazones (acylanthranils). General procedure. The all-glass apparatus comprised a 150-ml. round-bottom flask and a 10-inch Widmer column with electrically heated jacket, a condenser and a receiver with outlet protected by a calcium chloride tube. A mixture of 0.05 mole of N-acylanthranilic acid and 40.8 g. (0.4 mole) of 99–100% acetic anhydride was heated under total reflux for one hour, after which about 25 ml. was collected by slow distillation below 139°. Remaining acetic anhydride was removed under reduced pressure (water aspirator). On chilling the flask the residue solidified except in the case of formanthranil (isolation of which is outlined below) and in the trials which yielded no acylanthranils. The crude benzoxazone was dissolved in hot, dry[6] ethyl acetate, the solution was decolorized by Nuchar, and the filtered liquid was treated with *n*-hexane just short of turbidity and was chilled in an ice bath. A second crop was obtained by concentration of the mother liquor. The product was washed sparingly with cold ethyl acetate-*n*-hexane and was dried *in vacuo* over calcium chloride and paraffin shavings. In most cases a second crystallization yielded a pure product.

3,1,4-Benzoxazone (formanthranil). The dark viscous residue left after removal of acetic anhydride was distilled under 0.3 mm. pressure. The main portion distilled at 122° and solidified in the rece|ver, m.p. 43–44°. Formanthranil is readily hydrolyzed by atmospheric moisture. Upon standing in a stoppered flask for twenty-four hours a specimen showed the melting range 42–75°. Material kept in a drying pistol containing phosphorus pentoxide showed no change in melting point during seven days, but later acquired a yellow color and deteriorated. An attempt to obtain formanthranil by heating formylanthranilic acid with 99–100% formic acid (instead of acetic anhydride) was unsuccessful, and when formic acid was added to the usual reaction mixture (formylanthranilic acid and acetic anhydride) the general procedure yielded 3-(2′-carboxyphenyl)quinazolone-4, m.p. 274.5–275°. This was identified by analysis and later by mixed m.p. test (m.p. 273.5–274°) using a specimen of m.p. 276–277° prepared from N-anthranilylanthranilic acid[7] (30, 37). This compound is known to form (30) upon heating N-formylanthranilic acid under reduced pressure. Results of another unsuccessful attempt to make formanthranil are mentioned later.

2-Methyl-3,1,4-benzoxazone (acetanthranil) is best prepared from anthranilic acid and acetic anhydride by the general procedure. It should be crystallized with scrupulous exclusion of water, and may be purified also by sublimation at 70–75° and 0.03 mm. It should be stored in a desiccator.

Data for the twelve benzoxazones prepared in the manner described are presented in Table I. Only the first two were found to be noticeably affected by moisture; the others appear to be fairly stable compounds.

Benzoxazones were not obtained from the following N-acylanthranilic acids: isovaleryl, *n*-caproyl, lauryl, and 3,5-dinitrobenzoyl. The reaction residues were viscous and dark, and any solid materials isolated after prolonged operations were not benzoxazones. Thus isovalerylanthranilic acid gave a reaction mixture which after standing a month yielded some N-acetylanthranilic acid (m.p. 181–182°), formed probably by transacylation followed by incidental hydrolysis. From *n*-caproylanthranilic acid there was obtained a compound

[6] For the satisfactory purification of lower benzoxazones complete absence of water was found to be essential. Acetanthranil was dissolved for crystallization by heating with insufficient *n*-hexane (in which it is rather soluble) and adding ethyl acetate dropwise until a clear solution resulted.

[7] Heating with either formic acid or ethyl orthoformate converted anthranilylanthranilic acid to 3-(2′-carboxyphenyl)quinazolone-4 in high yield (44). By milder action of formic acid the product was *o*-formaminobenzoylanthranilic acid (m.p. *ca.* 211°; *Anal.*: Calc'd C, 63.3; H, 4.23; Found C, 63.4; H, 4.23) converted to the quinazolone (m.p. 276–277°) almost quantitatively on heating at the melting point. *Erratum.* In reference 37a, p. 63, Table I, column 2, following "anthranilic acid", the entry should be 150° instead of 50°.

of m.p. 144–144.5°, not identified (Analysis: C, 63.3; H, 5.91). From laurylanthranilic acid the only compound isolated was some unchanged starting material; 3,5-dinitrobenzoylanthranilic acid yielded some N-acetylanthranilic acid (m.p. 181–184°) by transacylation and hydrolysis.

Attempted use of acylanthranilic ester for benzoxazone synthesis. Methyl anthranilate, treated with acetic anhydride as in the general procedure, yielded only methyl N-acetylanthranilate. The same reactants, or methyl N-formylanthranilate and acetic anhydride, when heated at 200° yielded both methyl N-acetylanthranilate and methyl N,N-diacetylanthranilate. These results show that formylanthranilic ester suffered transacylation, and that considerable exhaustive acetylation occurred, but that conditions were not sufficiently severe to force ring closure.

Methyl N,N-diacetylanthranilate. Methyl N-formylanthranilate (10.0 g., 0.55 mole) and acetic anhydride (40.8 g., 0.4 mole) in a sealed tube were heated for six hours at 200°. After removal of acetic anhydride the residue yielded a product (3.5 g., melting range 60–78°) which after four recrystallizations from ethyl acetate-hexane melted at 66–67°. Analysis yielded data which indicate this compound to be methyl N,N-diacetylanthranilate.

Anal. Calc'd for $C_{12}H_{13}NO_4$: C, 61.3; H, 5.57; N, 5.60; Sap. equiv., 78.3; Neut. equiv., 0.
Found: C, 61.3; H, 5.46; N, 5.67; Sap. equiv., 78.1; Neut. equiv., 0.

It appears that the m.p. 180° reported for this compound by Erdmann (31), and which is unexpectedly high for an amide incapable of association,[8] may be incorrect. The product of m.p. 66–67° was obtained also in an experiment with methyl anthranilate and acetic anhydride, and the two were shown by mixed m.p. test to be identical. In both experiments the mother liquors, including those from the recrystallizations, were examined further, leading to the isolation of solid products both of which after several crystallizations melted 98–99°; a mixed m.p. test showed them to be identical. Identification as *N-acetylanthranilic methyl ester* was established by the m.p. (33) and by analysis.

Anal. Calc'd for $C_{10}H_{11}NO_3$: C, 62.1; H, 5.70.
Found: C, 62.2; H, 5.67.

Reactions of 3,1,4-benzoxazones with ammonia. The benzoxazone (0.01) mole) was dissolved in the minimal absolute ethanol at a suitable temperature and anhydrous ammonia was bubbled into the solution for about an hour. To obtain *o*-acylaminobenzamides (III) the reaction with ammonia was conducted at a temperature below that which induces ring closure to quinazolone (IV). The products were isolated by concentration of the alcoholic solutions, and were generally pure after one recrystallization from ethyl acetate-hexane. In the case of 3,1,4-benzoxazone (formanthranil) chilling in an ice-bath was required, and temperatures below or near room temperature are needed with 2-methylbenzoxazone (acetanthranil) (19), 2-ethylbenzoxazone, and *n*-propylbenzoxazone, all of which were converted to quinazolones by ammonia at the temperature of boiling ethanol. Interaction with ammonia in boiling ethanol yielded the appropriate *o*-acylaminobenzamides (III) in good yields from the following benzoxazones: *o*- and *p*-tolyl, *o*- and *p*-chlorophenyl, *o*- and *p*-nitrophenyl, and 3-pyridyl. Essential data for these acylaminobenzamides appear in Table II.

To obtain the *2-substitutedquinazolones* (IV) the isolated *o*-acylaminobenzamide, in an open flask, was heated for thirty minutes at 240–250° (20) in a bath of Wood's metal. The residue was dissolved in the minimal ethyl acetate, the solution was treated with Nuchar, and to the hot filtrate was added hexane short of turbidity. The crystalline product in most cases was pure after one recrystallization. Data for the several quinazolones are collected in Table III.

Quinazolones were obtained in one operation from benzoxazone (formanthranil), 2-methylbenzoxazone, 2-ethylbenzoxazone, and 2-*n*-propylbenzoxazone by action of ammonia in boiling ethanol. Ring closure failed to occur at 250° with the following *o*-acylaminobenzam-

[8] The monoacetyl ester, presumably capable of association (32), melts at 100–101° (33). The fact that disubstituted amides melt lower than monosubstituted amides is familiar (32, 34).

ides: *o*-toluyl, *o*-chlorobenzoyl, and *o*-nitrobenzoyl, apparently due to interference by *ortho* substituents.

Reactions of 3,1,4-benzoxazones with aniline. To prepare the *o*-acylaminobenzanilide (III) a mixture of the acylanthranil (0.01 mole) and aniline (0.011 mole) in an open flask was heated for three hours on a steam-bath. The product was recrystallized from ethyl acetate-hexane after decolorization with charcoal, and was then substantially pure. For analysis a specimen of constant melting point was submitted to an additional crystallization. Preparative and analytical data appear in Table IV.

To prepare the *3-phenylquinazolones* (IV) the *o*-acylaminobenzanilide (III), when R was an alkyl group, was heated to 240–250° for thirty minutes; when R was aromatic the acylaminobenzanilide (0.01 mole) was mixed with about 3 mg. of anhydrous zinc chloride and the mixture was heated at 240–250° until evolution of gas ceased (about ten minutes). In preliminary trials it was found that heat alone failed to cause ring-closure of *o*-toluylaminobenzanilide at 250° or even at 300°. In each case the cooled melt was dissolved in the least hot ethyl acetate, and *n*-hexane was added until crystallization was well started, when the mixture was chilled in an ice-bath. The crystals were washed with eight 15-ml. portions of 10% aqueous ammonia, and were pure after an additional decolorization and recrystallization; samples for analysis were crystallized a third time. Preparative and analytical data for 3-phenylquinazolones appear in Table V.

Preparation of *quinazolones from benzoxazones* in one operation by heating the latter with aniline at an intermediate temperature was successful in the two trials made. When 2-ethylbenzoxazone (0.01 mole) and aniline (0.011 mole) were mixed and heated to 150–160° for thirty minutes there resulted a 67.8% yield of 2-ethyl-3-phenylquinazolone-4 of m.p. 125–126°. Similarly 2-*n*-propylbenzoxazone yielded 2-*n*-propyl-3-phenylquinazolone-4.

The interaction of 3,1,4-benzoxazone with aniline at 100° or at 160–170° produced a dark viscous oil from which no solid could be isolated. Ring closure failed to occur when R (formula III) was *o*-chlorophenyl or *o*-nitrophenyl, and when R was *o*-tolyl the yield of quinazolone was only 16%, again suggesting interference by *ortho* substituents.

Transacylation experiments. During preparation of benzoxazones other than 2-methylbenzoxazone the reaction mixtures yielded no 2-methylbenzoxazone, a result which does not establish its complete absence, though the fairly high yields of the expected benzoxazones shows that transacylation was at most probably inconsiderable. *Catalyzed transacylation* of *N*-formylanthranilic acid was effected as follows. A mixture of *N*-formylanthranilic acid (4.95 g., 0.03 mole), acetic anhydride (24.4 g., 0.24 mole) and anhydrous sodium acetate (0.49 g., 0.006 mole) was treated as in the general preparative procedure. The sodium acetate was removed, and the liquid was concentrated by passage of a stream of dry air until solid material separated. This was crystallized from ethyl acetate-hexane after treatment with Nuchar. The product melted at 78–80° and was identified as 2-methylbenzoxazone (acetanthranil) by mixed m.p.; the yield was 2.12 g. (44.7%). A similar experiment using γ-picoline (0.47 g., 0.005 mole) as catalyst yielded 1.36 g. (28.1%) of acetanthranil (m.p.79–80°), identified by mixed m.p. test.

No evidence of transacylation was observed in similar experiments in which *N*-*n*-butyrylanthranilic acid or *N*-benzoylanthranilic acid was heated with acetic anhydride either alone or with sodium acetate, or in which *N*-*n*-butyrylanthranilic acid was heated with propionic anhydride. Attempts to convert 3,1,4-benzoxazone or 2-phenylbenzoxazone to 2-ethylbenzoxazone by heating with propionic anhydride yielded none of the transacylated product, only starting materials being recovered.

Ultraviolet absorption spectra. The instrument used was a Beckman spectrophotometer (35). The solvent was dioxane purified as described by Fieser (36) followed by distillation through a 24-inch Vigreux column. Isatoic anhydride (37) was purified by recrystallization from 95% ethanol, then from dioxane, and finally by sublimation (170–180° at 0.02–0.03 mm.); the m.p. was 239–243°. Acetanthranil (2-methyl-3,1,4-benzoxazone) was crystallized three times from ethyl acetate-hexane, then sublimed (70–75° at 0.03 mm.), and was used at once, m.p. 81–82°. N-Acetylanthranilic acid was crystallized five times from ethyl ace-

tate and was dried in an Abderhalden apparatus, m.p. 184–185°. Triethylamine (E. K. Co. No. 616) was dried for twenty-four hours over pellet-form potassium hydroxide and was then distilled, b.p. 87–88°. The values for log E_m given below were determined for the following côncentrations of solute: log E_m 1–2, 0.01 *M;* log E_m 2–3, 0.001 *M;* log E_m 3–4, 0.0001 *M;* log E_m 4–5, 0.00001 *M*. The wave lengths and intensities of the absorption maxima of isatoic anhydride, of isatoic anhydride in 0.01 *M* triethylamine solution, of 2-methyl-3,1,4-benzoxazone (acetanthranil), and of *N*-acethylanthranilic acid, are as follows.

COMPOUND	ABSORPTION WAVE LENGTH (m)	MAXIMA INTENSITY (LOG E_m)
Isatoic anhydride	315	3.58
	239	3.95
Isatoic anhydride in 0.01 *M* triethylamine	317	3.57
	242	3.96
2-Methyl-3,1,4-benzoxazone (acetanthranil)	305	3.54
	250	3.90
N-Acetylanthranilic acid	312	3.75
	252	4.14

Infrared absorption spectrum. Infrared absorption measurements were made with a Perkin-Elmer model 12B spectrometer. The sample of resublimed acetanthranil was melted on a salt plate for examination.

SUMMARY

1. A procedure is described for the preparation of 3,1,4-benzoxazones (acylanthranils) by dehydration of N-acylanthranilic acids with acetic anhydride. Eleven benzoxazones, eight of which are new, were so prepared. The method failed with the following N-acylanthranilic acids: isovaleryl, *n*-caproyl, lauryl, and 3,5-dinitrobenzoyl.

2. Transacylation by acetic anhydride was observed only with N-formylanthranilic ester and with several N-acylanthranilic acids which failed to yield benzoxazones. N-Formylanthranilic acid suffered transacylation by propionic anhydride, and by acetic anhydride in presence of sodium acetate or γ-picoline. Benzoxazones were not transposed by heating with unrelated acid anhydrides.

3. Under mild conditions 3,1,4-benzoxazones react with ammonia and with aniline to yield corresponding *o*-acylaminobenzamides and *o*-acylaminobenzanilides; sixteen of these not previously reported were made and characterized. By reaction at higher temperatures, or by heating N-acylaminobenzamides above 240°, or by so heating the N-acylaminobenzanilides in presence of zinc chloride, ring closure occurs yielding the 4-quinazolones; twelve new quinazolones are reported.

4. Certain of the results support the belief that the so-called acylanthranils have the benzoxazone structure.

PHILADELPHIA 4, PENNA.

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[Contribution from the Cobb Chemical Laboratory of the University of Virginia]

ANTIMALARIALS. α,β-DIMORPHOLINYL KETONES AND RELATED COMPOUNDS[1, 2]

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This work stemmed from the observation that 1,2-dibenzoyl-1-dibutylaminoethylene (I) retarded appreciably the growth of parasites in ducks infected with *Plasmodium lophurae*[4, 5] (1).

$$C_6H_5COCH{=}\underset{\displaystyle N(C_4H_9)_2}{\underset{|}{C}}COC_6H_5$$

I [SN[6]88; Q[7] = < 0.015]

Other analogs of this compound, made subsequently for comparative tests, seemed also to be slightly active,[5] especially the morpholinyl analog (2).[5]

To study the effect of deletion of the γ-carbonyl group from this type (I) samples of known α-(tertiary-amino)chalcones (benzalacetophenones) of the type II (4) were prepared and tested, and of these the α-diethylamino compound

[1] (a) The larger portion of the work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Virginia. Some parts of the work were supported by a subsequent grant-in-aid from the National Institutes of Health.

(b) The bulk of the work reported in this paper followed from the discovery of antimalarial activity in the compounds of the type I, II, and III through tests on samples submitted from this laboratory during the summer of 1942 to the Lilly Research Laboratories and to the National Institutes of Health. Since an extension of the studies on the type II and III compounds had been started earlier by Cromwell in 1940 [(4b), (4c), cf. (7)] this program (under O.S.R.D.) was limited to the development of the antimalarial lead, by way of synthesis of analogous compounds specifically for antimalarial tests.

[2] Acknowledgment: The synthesis of certain of the compounds reported were carried out by (a) P. S. Bailey, (b) J. A. Freek, (c) A. G. Howe, (d) J. F. Tinker, and (e) W. L. Yost.

[3] Present locations: (a) General Aniline and Film Corp., Easton, Pa., (b) National Institutes of Health, Bethesda, Md., (c) Deceased, (d) Southern Research Institute, Birmingham, Ala., (e) S. E. Massengill Co., Bristol, Tenn., (f) Chemical Abstracts, Columbus, Ohio, (g) Richmond Medical College, Richmond, Va., (h) Smith, Kline, and French Laboratories, Philadelphia, Pa.

[4] Carried out at the Lilly Research Laboratories.

[5] This compound is listed as "inactive" according to the standards set up in the Survey monograph [see (3)].

[6] The SN number (Survey number) identifies the drug in the Wiselogle Monograph [see (3)].

[7] Quinine equivalents [see (3)] unless otherwise specified were determined against *P. gallinaceum* in the chick, at the National Institutes of Health under the direction of Dr. G. Robert Coatney.

showed indication of slight activity,[5] as also did the α-morpholinyl compound (II).[6]

$$\begin{array}{ll} C_6H_5CH{=}\underset{\displaystyle NC_4H_8O}{\underset{|}{C}}COC_6H_5 & \qquad C_6H_5\underset{\displaystyle OC_4H_8N}{\underset{|}{CH}}{-}\underset{\displaystyle NC_4H_8O}{\underset{|}{CH}}COC_6H_5 \\ \text{II}\ \ [\text{SN } 1623; Q = < 0.03] & \qquad \text{III}\ \ [\text{SN } 2623; Q = 0.1] \end{array}$$

Related compounds in this field, α-mono-(tertiary-amino)-β-phenylpropiophenone (5), $C_6H_5CH_2CH(N\langle\ \rangle)COC_6H_5$, the β-analogs, $C_6H_5CH(N\langle\ \rangle)CH_2$-$COC_6H_5$ (5), and α,β-dipiperidyl-β-phenylpropiophenone (an analog of III) (4a, 6), were inactive, but α,β-dimorpholinyl-β-phenylpropiophenone (III) (4c) was found to be definitely "active" (3), being one-tenth as active as quinine against *P. gallinaceum* in the chick.[7, 8]

Since antimalarial activities of Q = 0.015–0.06 were found in numerous other compounds of the type (III), whereas no activity was observed in analogs carrying tertiary-amino groups other than morpholine, efforts were directed toward the substitution of groups in one or both phenyl nuclei. Thirty new α,β-dimorpholinyl-β-phenylpropiophenones have been made, and are listed in Table I. These involve as substituent groups, alkyl, phenyl, halogen, alkoxyl, nitro, acetamido, and carbethoxyamino; and of these, nine derivatives proved to be definitely "active" but none was as active as the first of the type to be tested, namely, III itself.

The dimorpholinyl ketones were made from the corresponding chalcones (Table II) by the action of morpholine on the dibromides (Table III); [*cf.*, (7)]. Only in the parent series and in one other to be reported later, were the stereoisomers obtained, but in several cases there was observed the formation of the α-morpholinylchalcone (*cf.* II). The aryl substituent influenced the relative yields of the latter type compound in about the way that would be expected. Where the 4′-substituent (in the phenyl next to the keto group) was alkyl, phenyl, acetamido, carbethoxyamino, or alkoxyl, the dimorpholinyl ketone of type III was the only product isolated except in the single case of the 4′-phenyl compound where, along with a 91% yield of the expected product, there was obtained an 8% yield of the α-morpholinylchalcone of the type II. On the other hand, a 4′-chlorine or bromine decreased the yields of the dimorpholinyl product and increased the yields of the α-morpholinylchalcone to 31% and 38% respectively; and the 4′-nitro group brought the yield of the α-morpholinylchalcone up to 81% and lowered the yield of the dimorpholinyl ketone to 12%. These results are explainable in terms of electron displacement toward the *para* halogen or *para* nitro group and the increased stabilization of the α,β-unsaturated ketone system of the α-morpholinylchalcone structures.

The nineteen new chalcones listed in Table II were obtained in widely varying yields. Some of them, especially those carrying a *para*-nitrogen, were made with

[8] Tested against *P. lophurae* in the duck (Q = 0.03) at the Johns Hopkins Medical School under the direction of Dr. E. K. Marshall, Jr.

TABLE I

THE α,β-DI-(TERT-AMINO)-β-PHENYLPROPIOPHENONES AND THE α- (AND β-)-(TERT-AMINO) BENZALACETOPHENONES (CHALCONES)

(Ar-C-C-CO-Ar′)

SN[a] (OR DR)	SUBSTITUENTS[b]	PREP. METHOD	REACT. TIME (HRS.)	YIELD, %	M.P., °C. (CORR.)	NO.[c] IN TABLE IV
	A. THE α,β-DIMORPHOLINYL-β-PHENYLPROPIOPHENONES (TYPE III)					
3296	4′-Methyl	A[g]	2	24[e]	165–166	1
3295	4′-Isopropyl[f]	E	1	25[e]	176–177	2
4048	4′-*tert*-Butyl	A	1	79	176–177	3
4049	4′-Cyclohexyl	A[g]	1	30[e]	190–191	4
4045	4′-($CH_2CH_2C_6H_5$)	A	3	22[e]	175–176	5
—	4′-Phenyl[h]	C	24	91	184–186	6
6637	4′-Chloro[h]	C	24	61	162–163	7
4047	4′-Bromo[h]	C	10	52	158–159	8
—	4′-Nitro[h]	C	12	12	166–167	9
15,487	4′-$NHCOCH_3$	B, J	10	36[e]	201–202	10
15,665	4′-$NHCOOC_2H_5$	B	10	80	182–183	11
3110	4′-Methoxy	B[g]	16	58[i]	167–168.5	12
3639	4′-Ethoxy	A	3	86	173–174	13
4671	4′-*n*-Propoxy	B	24	63[i]	157[d]	14
4676	4′-Isopropoxy	B	24	89	157	15
4125	4′-*n*-Butoxy	B[g]	48	44[i]	162–163	16
3642	4′-Phenoxy	A	3	54	153–155	17
3759	4-Isopropyl	A	3	43[i]	181–183[d]	18
6637	4-Chloro	A	1	15[i]	165–165.5	19
3637	3-Methyl	A	2.5	40[e]	173–174	20
3093	3-Nitro	B[g]	2	45[j]	178	21
9169	2-Methoxy	A	3	70	175–176	22
3638	2′,5′-Dimethyl	A	3	31[e]	163–165[d]	23
3540	2′,4′-Diisopropyl	A	1	63	147–148	24
4669	3′,4′-Dichloro	B	B	23[e]	164–165	25
4903	5-Bromo-2′,4′-dimethoxy[18]	A[f]	—	—[f]	166–166.5	26
4677	4,4′-Dimethoxy	A	1.5	41[i]	178–179	27
4906	4′-Chloro-3′-methyl	B	3	16[e]	169–170	28
3641	4′-Isopropyl-4-methoxy	A	3	69	174[d]	29
4667	2′,4′,6′-Trimethyl	A	3	47	179–180	30
	B. THE α,β-DIPIPERIDYL-β-PHENYLPROPIOPHENONES					
—	3-Methylpiperidyl	B[n]	10	7	144–146	31
9020	4-Methylpiperidyl	B[n]	10	61	151[p]	32
3112	4′-Methoxy	B[g]	4	58	143–145.5	33
4063	4′-Phenoxy	A	2	81	165	34
	C. AN α,β-BIS-(TETRAHYDROISOQUINOLYL)-β-PHENYLPROPIOPHENONE					
4064	4′-Methoxy	B	—	40[i]	152–153	35

TABLE I—*Concluded*

SN[a] (OR DR)	SUBSTITUENTS[b]	PREP. METHOD	REACT. TIME (HRS.)	YIELD, %	M.P., °C. (CORR.)	NO.[c] IN TABLE IV
	D. OTHER α,β-DI(SUBSTITUTEDAMINO)-β-PHENYLPROPIOPHENONES					
6416	β-Anilino-α-benzylmethylamino	F	24	24[i]	133–134	36
5031	α-Benzylmethylamino-β-morpholinyl	F	10	30[i]	159	37
4678	α-Benzylmethylamino-β-methylanilino	F	9	68[i]	145	38
4904	β-Anilino-α-morpholinyl	G[g]	0.3	85	187–189	39
4902	β-Methylanilino-α-morpholinyl	G	5	53	168–169	40
	E. THE α-MORPHOLINYLBENZALACETOPHENONES (CHALCONES) (TYPE II)					
1623	None[f]	H	—[f]	—[f]	93	41
—	4′Phenyl[k]	D	24	8	142–144	42
3549	4′-Chloro[k]	D	24	31	108	43
6975	4′-Bromo[k]	D	10	38	105–106	44
—	4′-Nitro[k]	D	12	81	147–148	45
	F. THE β-(TERT.-AMINO)BENZALACETOPHENONES (TYPE V)					
3548	β-Morpholinyl[l]	I[m]	—	76	94–95	46
3260	β-Piperidyl	I	—[f]	52[f]	80–81	47
			—[f]	—	101–102	48

[a] Survey Number (see footnote[6]); the five-digit numbers are DR = drug repository, National Institutes of Health. [b] For quinine equivalents see (3). [c] Refers to analyses listed in Table IV. [d] Melts with decomposition. [e] These yields refer to highly purified material. [f] See experimental section. [g] Absolute ethanol was used as the reaction solvent. [h] For the data on the other product isolated from this reaction, see D. [i] Yield after one recrystallization. [j] Yield after several washings with ethanol. [k] For the data on the other product isolated from this reaction, see C. [l] Originally prepared (4c) by heating dibenzoylmethane with excess morpholine; m.p. 96–97°. A mixture melting point of samples prepared in the two ways showed no depression. Acid hydrolysis gave dibenzoylmethane. [m] Distilled β-methoxybenzalacetophenone was used as starting material. [n] Allowed to stand overnight in the refrigerator. [p] Solubility: in water at 25°, 0.05 g. per 100 ml.; at 90°, 0.1 g. per 100 ml.; in 3 N HCl at 25°, 1.0 g. per 100 ml.

the high antibacterial activity of benzalacetophenone and dibenzoylethylene in mind [*cf.* (8)].[9]

Absorption spectra of six of these compounds[10] over the wavelength range

[9] The following tests on substituted chalcones were carried out at the Lilly Research Laboratories. The 4-dimethylamino- and 4-diethylamino-chalcones and their 4′-ethoxycarbamino and 4′-acetamido derivatives showed little or no significant bactericidal, bacteriostatic or fungicidal activity. The 4-dimethylaminochalcone and three compounds of Table II (nos. 62, 64, 65) showed no significant antihistamine activity. The 4-dimethylaminochalcone and its 4′-ethylcarbamino derivative showed negligible ergotrate activity, and were not effective against tuberculus bacilli *in vitro*.

[10] The absorption spectra and interpretations of them were made by Dr. Henry Hemmindinger of the General Aniline and Film Corp., Easton, Penna.

600–220 mμ are shown in Figures 1 and 2 [*cf.* also (9)]. Over the concentration range studied there was no dependence of extinction coefficient on concentration.

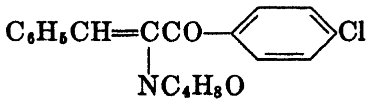
TABLE II

THE CHALCONES: ArCH=CHCOAr′

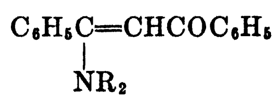
SUBSTITUENT	PREP.[a] METHOD	REACT. TIME (HRS.)	CRYST. FROM[b]	YIELD, %	M.P. OR B.P., C. (CORR.)	NO. IN TABLE IV
4′-Cyclohexyl	A	—	EtOAc	90	124[i]	49
4′-$CH_2CH_2C_6H_5$	A	6	Ethanol	77	117[i]	50
4′-$NHCOCH_3$ (14)	A	2	Ethanol	63	160–161[k]	51
4′-$NHCOOC_2H_5$	A[c]	1	Ethanol	81	143–145[i]	52
4′-$NHCONH_2$	A	0.5	Diox. EtOH	53	217–218[k]	53
4′-*n*-Propoxy	A	2	Ethanol	71	76[i]	54
4′-Isopropoxy	A	3	Ethanol	23[d]	87[i]	55
4′-*n*-Butoxy	A	3	Ethanol	98	67–68[j]	56
4-$N(C_2H_5)_2$[f]	D[e]	3	[f]—	56	260–265[g, l]	57
2′,5′-Dimethyl[f]	B	2.5	[f]—	77	203–204[h]	58
3′,4′-Dichloro	A	1	Abs. EtOH	85	115–116[i]	59
4′-Chloro-3-methyl	A	2	Ethanol	81	106[i]	60
4′-Isopropyl-4-methoxy	A	2.3	Ethanol	89	71–72[j]	61
4′-$NHCOCH_3$-4-$N(CH_3)_2$	C	0.5	Acet. CH_3OH	54	204–205[k]	62
4′-$NHCOCH_3$-4-$N(C_2H_5)_2$	C	0.5	Butanone	75	157–158[k]	63
4′-$NHCOOC_2H_5$-4-$N(CH_3)_2$	D	2	Butanone	67	188–189[l]	64
4′-$NHCOOC_2H_5$-4-$N(C_2H_5)_2$	D	3	Butanone	68	157–159[l]	65
4′-$NHCONH_2$-4-$N(CH_3)_2$	A	1	Acet. EtOH	26	218–220[l]	66
4′-[$N{=}CHC_6H_4N(CH_3)_2$-(*p*)]-4-$N(CH_3)_2$	E	0.2	Acet. EtOH	—	223–225[l]	67

[a] See procedures in experimental section. [b] Solvent abbreviations: EtOAc = ethyl acetate; diox. = dioxane; EtOH = ethanol; acet. = acetone; but. = butanone. [c] Prepared also by the action of ethyl chlorocarbonate upon 4′-aminochalcone. [d] Also a 16% recovery of 4′-isopropoxyacetophenone; b.p. 78°/6 mm. [e] The reaction mixture was worked up according to B. [f] Oils. [g] B.p. at 7 mm. [h] B.p. at 1 mm. [i] Colorless. [j] Pale yellow. [k] Yellow. [l] Orange.

Among the few α-morpholinylchalcones (type II) studied, one, the 4′-chloro compound (IV), showed definite activity (Q = 0.03). The parent compound II



IV



V

was the only other compound of the type tested at comparable dosage and it was "inactive".

The isomeric β-morpholinylchalcone (V) and the β-piperidyl analog [*cf.* (7a)] were also made for comparison, but they were inactive (Q = <0.015); they were prepared by a new and improved method, from $C_6H_5C(OCH_3){=}CHCOC_6H_5$; this is essentially the method of Dufraise and Netter (10) which had been successfully applied to α-bromo-β-methoxychalcone.

In connection with the foregoing studies attempts were made to use substituted morpholines and piperidines in the reaction with chalcone dibromide. A number of mono- and dialkyl-morpholine derivatives were supplied by Dr. W. S. Cottle (11).[11] These were of particular interest in view of the seeming specificity for antimalarial activity of the morpholinyl group in this class of compounds, but unfortunately in our hands none of them gave crystalline prod-

TABLE III

THE CHALCONE DIBROMIDES: ArCHBrCHBrCOAr′

SUBSTITUENT	YIELD, %	CRYST. FROM[a]	M.P., °C. (CORR.)	EMPIRICAL FORMULA	NO. IN TABLE IV
4′-Isopropyl [*cf.* (15)]	91[e]	Acet. CH_3OH	143	$C_{18}H_{18}Br_2O$	68
4′-*tert*-Butyl	77[f]	Abs. EtOH	139.5–142	$C_{19}H_{20}Br_2O$	69
4′-Cyclohexyl	90[f]	—[j]	155–158	—	70
4′-$Ch_2CH_2C_6H_5$	96[e]	Ethanol	130–131	$C_{23}H_{20}Br_2O$	71
4′-Phenyl	90[g]	Acet. EtOH	195–196	$C_{21}H_{16}Br_2O$	72
4′-Chloro	98[f]	$ChCl_3$	192	$C_{17}H_{15}Br_2NO_2$	73
4′-$NHCOCH_3$ (16)[b]	62[f]	Ethanol	176–177[d]	$C_{17}H_{11}Br_2ClNO$	74
4′-$NHCOOC_2H_5$	81[e]	CCl_4	201–202[d]	$C_{18}H_{17}Br_2NO_3$	75
4′-*n*-Propoxy	93[e]	Ethanol	149	$C_{18}H_{18}Br_2O_2$	76
4′-Isopropoxy	48[h]	Ethanol	131	$C_{18}H_{18}Br_2O_2$	77
4′-*n*-Butoxy	62[e]	Ethanol	153–154	$C_{19}H_{20}Br_2O_2$	78
3-Methyl (17)[c]	86[e]	CH_3OH	123–124[c]	$C_{16}H_{14}Br_2O$	79
2-Methoxy	98[e]	Pet.-CCl_4	123–124	$C_{16}H_{14}Br_2O_2$	80
2′,5′-Dimethyl	77[f, i]	Ethanol	103–104	$C_{17}H_{16}Br_2O$	81
2′,4′-Diisopropyl	52[e]	Ethanol	124–125	$C_{21}H_{24}Br_2O$	82
3′,4′-Dichloro	80[e]	CCl_4	166–167	$C_{15}H_{10}Br_2Cl_2O$	83
4′-Chloro-3′-methyl	95[f]	Ethanol	146–147	$C_{16}H_{13}Br_2ClO$	84
4′-Isopropyl-4-methoxy	66[e, h]	CH_3OH	111–112	$C_{19}H_{20}Br_2O_2$	85
4,4′-Dimethoxy	98[e]	Benzene	147–148[d]	$C_{17}H_{16}Br_2O_3$	86

[a] Solvent abbreviations: acet. = acetone; EtOH = ethanol; pet. = petroleum ether. [b] Giua and Bagiella (16) described this compound as yellow prisms of m.p. 175°; our sample was colorless (rectangular prisms). [c] Giua (17) originally prepared this compound and reported the m.p. 127–128°. [d] Melts with decomposition. [e–h] Reaction solvents were [e] Carbon tetrachloride; [f] Chloroform; [g] Chloroform-ether mixture; [h] Absolute ether. [i] Cold ligroin added to precipitate the crude product. [j] Analytical sample not prepared.

ucts in this reaction. Partial success was achieved in the reactions with substituted piperidines.[11] In a series of comparable experiments, piperidine itself gave the α,β-dipiperidyl ketone in 69% yield (purified), and the α,β-bis-(4-methylpiperidyl) analog was obtained in 61% yield; the bis-(3-methylpiperidyl)ketone was obtained in smaller yield (27%), but no satisfactory products were isolated when 2-substituted piperidines were used, namely, the 2-methyl-, 2,4- and 2,6-dimethyl-, and 2,4,6-trimethyl-piperidines. Doubtless steric effects are operating in the latter cases, as would be expected.

[11] The substituted morpholines were furnished by Dr. W. S. Cottle (11) and the substituted piperidines by the C.M.R. group of Columbia University under Dr. R. C. Elderfield.

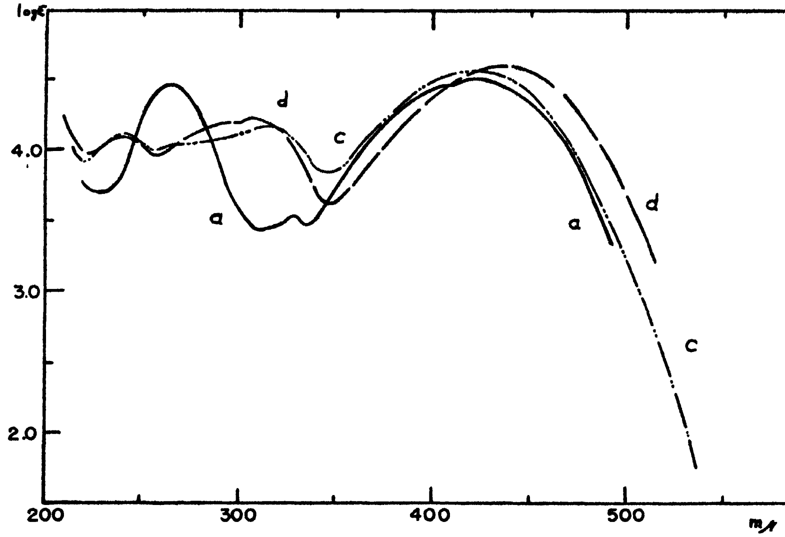


FIG. 1

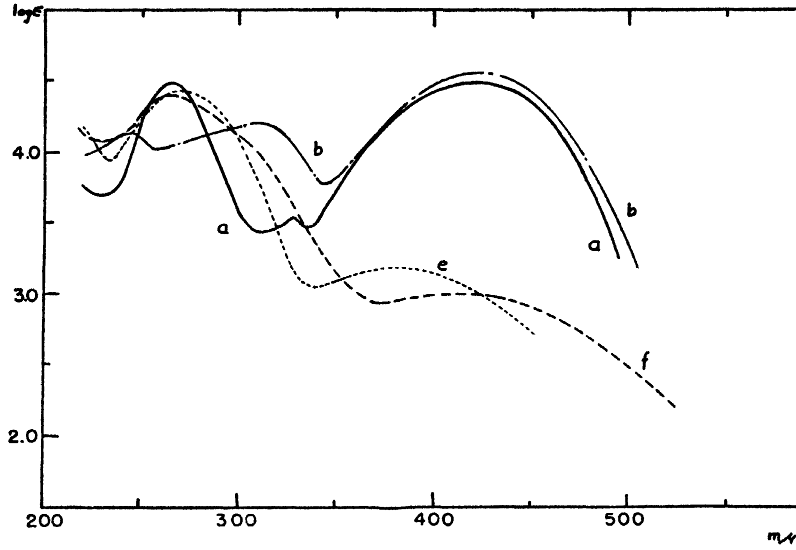


FIG. 2

FIGURES 1–2. ABSORPTION SPECTRA OF SIX CHALCONE DERIVATIVES

(a) ———— (p)-$(CH_3)_2NC_6H_4CH{=}CHCOC_6H_5$ [See (9)]

(b) —— · —— · —— (p)-$(CH_3)_2NC_6H_4CH{=}CHCOC_6H_4NHCOCH_3$-(p) (Table II, No. 62)

(c) —— · · —— · · —— (p)-$(CH_3)_2NC_6H_4CH{=}CHCOC_6H_4NHCOOC_2H_5$-(p) (Table II, No. 64)

(d) —— —— —— —— (p)-$(C_2H_5)_2NC_6H_4CH{=}CHCOC_6H_4NHCOCH_3$-(p) (Table II, No. 63)

(e) · · · · · · · $C_6H_5CH{=}C$(morpholinyl)COC_6H_4Br-(p) (Table II, No. 44)

(f) – – – – – – $C_6H_5CH{=}C$(morpholinyl)$COC_6H_4NO_2$-(p) (Table II, No. 45)

These determinations[10] were made in methanol at concentrations between 0.002 and 0.2 g. per liter and path lengths of 10.0 to 0.1 cm.; the half width of the dispersed beam transmitted by the Cary recording spectrophotometer was less than 0.5 mμ. over the entire range.

Attempts to obtain crystalline diamino ketones using diethyl- and dibutylamines were not successful.

One of the structural changes considered, relative to III, was the deletion of one of the phenyl groups with substitution of hydrogen or of an alkyl. The tertiary-butyl analog (VI) made from benzalpinacolone proved to be active.

$$\begin{array}{cc} C_6H_5CH{-}CHCOC(CH_3)_3 \\ \quad | \qquad\qquad | \\ OC_4H_8N \qquad NC_4H_8O \end{array} \qquad \begin{array}{cc} XC_6H_4CH{-}CHCOCH_3 \\ \quad | \qquad\qquad | \\ OC_4H_8N \qquad NC_4H_8O \end{array}$$

VI [SN 3107; Q = 0.06]

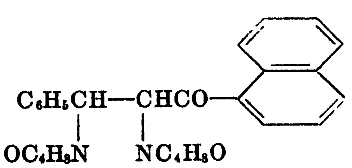
VII (a) X = H; (b) X = *p*-Cl; (c) X = *p*-Br.

The benzylacetone analog and its *p*-chloro and *p*-bromo derivatives (VII), prepared in the usual way [*cf.* (7)], were inactive. The *p*-chloro- and *p*-bromopropiophenone analogs (X) [*cf.* (12)] (also inactive) were prepared by the action of morpholine on the dibromo compounds (IX), which were made by the method of Kohler (13) through α,β-dibromopropionyl chloride (VIII) by the Friedel-Crafts reaction, as shown in VIII–X.

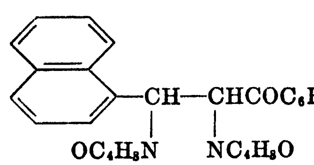
$$CH_2BrCHBrCOCl \longrightarrow CH_2BrCHBrCOC_6H_4X \longrightarrow \begin{array}{c} CH_2CHCOC_6H_4X \\ | \qquad | \\ OC_4H_8N \quad NC_4H_8O \end{array}$$

VIII IX X (a) X = *p*-Cl; (b) X = *p*-Br.

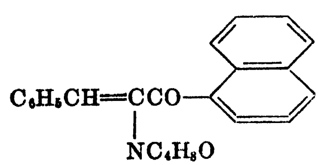
One other major structural variation relative to III was the substitution of a naphthyl residue for one of the phenyls. α,β-Dimorpholinyl-β-phenyl-1-propionaphthone (XI) and its structural isomer (XII) were synthesized, and also the 2-naphthyl analog of XI, and α-morpholinyl-β-phenyl-1-acrylonaphthone (XIII). These compounds were inactive (Q = <0.015).



XI



XII



XIII

To test the specificity of the α,β-dimorpholinyl ketone system of III, the α,α'-dimorpholinyl ketone (XIV) was made through 2,4-dibromo-1,5-diphenyl-3-pentanone; it was inactive. An attempt to make the β,β'-dimorpholinyl analog of XIV by the addition of morpholine to dibenzalacetone gave only the monomorpholinyl addition product (XV).

$$C_6H_5CH_2CH(NC_4H_8O)COCH(NC_4H_8O)CH_2C_6H_5$$

XIV [SN 4670; Q = 0.03]

$$C_6H_5CH(NC_4H_8O)CH_2COCH{=}CHC_6H_5$$

XV

Incidental to this research several Mannich reactions were carried out on *p*-chloro- and *p*-bromo-benzalacetone; the products (type XVI) were ineffective against malaria.

$$X\text{-}C_6H_4\text{-}CH{=}CHCOCH_2CH_2\overset{+}{N}HR_2\ \overset{-}{Cl}$$

XVI

Acknowledgment. The absorption spectra reported in Figures 1 and 2 were determined by Dr. Henry Hemmindinger.

EXPERIMENTAL[12]

THE α,β-DI-(TERTIARY-AMINO)-β-PHENYLPROPIOPHENONES AND THE α- (AND β) (TERTIARY-AMINO)CHALCONES

Procedure A. α,β-Dimorpholinyl-β-(m-tolyl)propiophenone. Morpholine (50 g.; 0.52 mole) was added slowly to a stirred solution of 39 g. (0.1 mole) of 3-methylchalcone dibromide (14) in 150 ml. of acetone. The mixture was refluxed for 2.5 hours, cooled to 5°, and filtered to remove morpholine hydrobromide. Evaporation under a stream of air and addition of 50 ml. of ligroin brought about crystallization of the crude product; it was washed with small portions of cold ligroin and with water, and was crystallized once from benzene-ligroin (9:1) mixture and twice from methanol; 16 g. (40%).

Procedure B. 4′-Acetamido-α,β-dimorpholinyl-β-phenylpropiophenone. A mixture of 30 g. (0.07 mole) of 4′-acetamidochalcone dibromide, 30.5 g. (0.35 mole) of morpholine, and 400 ml. of acetone was allowed to stand at room temperature for 10 hours. Filtration gave 23 g. (97%) of morpholine hydrobromide. Concentration of the yellow filtrate under reduced pressure, slurrying with water and filtering, gave 31 g. of yellow solid; m.p. 160–164°. This was digested with 400 ml. of boiling ligroin and filtered while hot (29 g.; m.p. 165–170°); the process was repeated with boiling 90% ethanol (13 g.; m.p. 194–196°). Recrystallization from 400 ml. of absolute ethanol gave 11 g. (36%); pale yellow needles; m.p. 199–201°.

Procedure C. 4′-Bromo-α,β-dimorpholinyl-β-phenylpropiophenone. Morpholine (22 g.; 0.25 mole) was added to a suspension of 22 g. (0.05 mole) of 4′-bromochalcone dibromide in 250 ml. of acetone, with cooling. The resulting orange solution was allowed to stand at room temperature for 10 hours, filtered from the almost theoretical yield of morpholine hydrobromide, and concentrated under reduced pressure; the resulting orange precipitate was washed with water, slurried with 400 ml. of petroleum ether, and filtered; 14 g. (52%).

Procedure D. 4′-Bromo-α-morpholinylchalcone. The final petroleum ether filtrate (above) upon evaporation under reduced pressure gave 7 g. (38%) of orange solid. Two recrystallizations from ethanol and three from hexane gave a pure product; orange rectangular prisms.

Procedure E. α,β-Dimorpholinyl-β-phenyl-p-isopropylpropiophenone. Morpholine (30 g.; 0.34 mole) was added to a stirred suspension of 27 g. (0.066 mole) of 4′-isopropylchalcone dibromide in 200 ml. of absolute ethanol, and the mixture was stirred at 35° for one hour. Cooling to 0° gave an orange precipitate which was washed successively with a little cold ethanol and water; 12 g.; m.p. 158–163°. Recrystallization from ethanol gave 7 g. (25%); very pale yellow solid.

[12] All melting points are "corrected".

Procedure F. α-(Benzylmethylamino)-β-N-methylanilino-β-phenylpropiophenone. A mixture of 12.3 g. (0.03 mole) of β-(benzylmethylamino)-α-bromo-β-phenylpropiophenone (18), 30 ml. of absolute ethanol, and 6.3 g. of methylaniline was warmed slightly to dissolve all of the materials; it was allowed to stand at room temperature for 9 hours and was cooled. The resulting precipitate was crystallized from 800 ml. of methanol; 8.9 g. (68%); m.p. 144–145°.

Procedure G. β-N-Methylanilino-α-morpholinyl-β-phenylpropiophenone. A mixture of 25 g. of α-bromo-β-morpholinyl-β-phenylpropiophenone (5), 15.5 g. of methylaniline, and 55 ml. of methanol was refluxed for 5 hours. Cooling precipitated 14 g. (53%); m.p. 137–142°.

Procedure H. α-Morpholinylchalcone [*cf.* 4c] was prepared without isolation of intermediates as follows: Bromine (54 g.; 0.337 mole) was added dropwise under cooling to a stirred solution of 70 g. (0.336 mole) of chalcone in 250 ml. of absolute ethanol, and one equivalent of sodium ethoxide (from 7.7 g. of sodium and 100 ml. of ethanol) was added. After refluxing for one hour and cooling, 44 g. of morpholine was added and the mixture was allowed to stand overnight. A second equivalent of sodium ethoxide was added and the mixture was refluxed for two hours. Concentration under reduced pressure and washing the orange precipitate with water gave 60 g. (61%); m.p. 89–93°.

Procedure I. A new higher-melting form of β-piperidylchalcone. A mixture of 10 g. of distilled β-methoxychalcone (19, 20), 8 g. of piperidine, and 40 ml. of ethanol was refluxed for fifteen minutes. The product, isolated by addition of water, melted at 101–102°; it was hydrolyzed by 25 ml. of 80% ethanol and 0.3 ml. of conc'd hydrochloric acid (refluxing for 15 minutes), to dibenzoylmethane (identified by mixture m.p.).

The *lower-melting form,* evidently identical with that reported by André (21), was obtained in an experiment carried out several years later, as follows: A solution of 5.75 g. (0.25 mole) of sodium in 100 ml. of methanol was added to a stirred suspension of 46 g. (0.125 mole) of chalcone dibromide in 100 ml. of methanol. The mixture was refluxed for one hour, allowed to cool, treated with 32 g. (0.375 mole) of piperidine, refluxed for forty-five minutes, and poured into water. The partly crystalline precipitate was washed with water, dried, and slurried several times with petroleum ether; 19 g. (52%) of pale yellow solid; m.p. 80–81°. Recrystallization from ethyl acetate-petroleum ether mixture did not change the melting point. André (21) reported the m.p. 81°.

Repetition of the first preparation from distilled β-methoxychalcone gave the higher-melting form (m.p. 101–102°).

Seeding the lower-melting form in solution or in the pulverized solid form caused conversion to the higher-melting form, but attempts to bring about change in the opposite direction were unsuccessful.

5(?)-Bromo-2,4-dimethoxy-α,β-dimorpholinyl-β-phenylpropiophenone (Table I, No. 26)[13] was made from the crude non-crystalline product of the bromination of 2′,4′-dimethoxychalcone (22) in 4:1 carbon tetrachloride-ether mixture at 10°. Purification of the crude product gave only a very small yield of pure compound which contained halogen. It is evident that the desired compound, doubtless the main product, was eliminated in the purification procedure and the much less soluble by-product (brominated in the nucleus) was the one isolated. The exact location of the bromine (assumed) was not checked by direct evidence.

4′-Acetamido-α-bromochalcone. A mixture of 30 g. (0.07 mole) of 4′-acetamidochalcone dibromide, 12.5 g. (0.092 mole) of sodium acetate, and 200 ml. of ethanol was refluxed for six hours. Addition of water and extraction with ether gave 15 g. (m.p. 153–156°); after repeated crystallizations from ethanol and isopropanol, m.p. 154–155°.

Anal. Calc'd for $C_{17}H_{14}BrNO_2$: C, 59.32; H, 4.10; N, 4.07.

Found: C, 59.36; H, 4.06; N, 4.10.

The dimorpholinyl ketone (see Table I) was obtained by the action of morpholine on

[13] This compound was erroneously reported to the Wiselogle Monograph (3) as the bromine-free compound (SN 4903).

either (a) the oil obtained by concentrating the ether extract (above), or (b) the isolated α-bromochalcone.

α-Bromo-β-morpholinyl-β-(4-methoxyphenyl)propiophenone, $(p)CH_3OC_6H_4CH(NC_4H_8O)$-$CHBrCOC_6H_5$, was isolated in an unsuccessful attempt to prepare the corresponding α,β-dimorpholinyl ketone. The structure is suggested on the basis of analogy (7).

A solution of 15 g. of 4-methoxychalcone dibromide (23), 200 ml. of ethanol, and 19.6 g. (6 equivalents) of morpholine was allowed to stand at room temperature for twenty-four hours, concentrated to one-third its volume and cooled; the resulting oil solidified slowly and was washed with ether and with water; 13 g., m.p. 72.5–74°; after six crystallizations from ethanol, m.p. 73.5–74°.

Anal. Calc'd for $C_{20}H_{22}BrNO_3$: C, 59.42; H, 5.49.
Found: C, 59.60; H, 5.88.

A second run (under reflux for four hours) gave 1.7 equivalents of morpholine hydrobromide but otherwise only resinous products.

α,β-Dimorpholinyl- and dipiperidyl-β-phenylpropiophenones (*cf.* III) (4, 6b, 7) were prepared by slowly adding five equivalents of the amine to a cooled suspension of chalcone dibromide in acetone, and allowing the mixtures to stand overnight (*cf.* Procedure C above).

NUCLEAR-SUBSTITUTED BENZALACETOPHENONES (CHALCONES)

Procedure A. 3′,4′-Dichlorochalcone. Sodium hydroxide (100 ml.; 20%) was added slowly under stirring to a mixture of 65 g. (0.344 mole) of 3,4-dichloroacetophenone (24), 37 g. (0.349 mole) of benzaldehyde, and 300 ml. of ethanol, at a maintained temperature of 15–30°. Within one hour the mixture thickened and stirring became ineffective. After standing for ten hours at 2–5°, the pale yellow product was filtered, washed free of alkali with water, and finally was washed with 40 ml. of cold ethanol; 81 g. (85%); m.p. 110–112°. Three recrystallizations, once from benzene and twice from absolute ethanol, gave a pure product.

Procedure B. 2′,5′-Dimethylchalcone. To a cooled mixture of 60 g. (0.41 mole) of 2,5-dimethylacetophenone, 80 ml. of 20% sodium hydroxide, and 275 ml. of ethanol, was added 42.9 g. (0.41) mole) of benzaldehyde under stirring and at such a rate that the reaction temperature did not exceed 27°. Stirring was continued for 2.5 hours. The oil was separated, washed, and fractionated; b.p. 203–204°/1 mm.; n_D^{25} 1.6300; 75 g. (77%).

Procedure C. 4′-Acetamido-4-dimethylaminochalcone. A mixture of 35.4 g. (0.2 mole) of 4-acetamidoacetophenone, 30 g. (0.2 mole) of 4-dimethylaminobenzaldehyde, 100 ml. of 20% sodium hydroxide, and 500 ml. of methanol at 30–45° was stirred for thirty minutes or until solution occurred. After cooling and standing overnight the orange precipitate was washed free of alkali, and dried; 33 g. (54%) m.p. 194–197°. Recrystallization from acetone-methanol yielded 20 g. of yellow rectangular prisms.

Procedure D. 4′-Carbethoxyamino-4-dimethylaminochalcone (ethyl 4[(p-dimethylaminocinnamoyl)phenyl]carbanilate). A solution of 11 g. of sodium in 200 ml. of methanol was added to a stirred mixture of 82 g. (0.4 mole) of purified ethyl 4-acetylcarbanilate, 60 g. (0.4 mole) of freshly recrystallized 4-dimethylaminobenzaldehyde, and 800 ml. of methanol. Upon refluxing for ten minutes a red solution resulted, and during two hours of refluxing an orange solid separated. Filtering while still warm, washing with water and with methanol, gave 84 g. (67%); m.p. 187–189°. Recrystallization from 1 liter of butanone gave a pure product; orange colored, 62 g., m.p. 188–189°.

This reaction when carried out at 40–45° for one hour, was incomplete. At first it was suspected that at higher temperatures cleavage of the ethyl carbanilate system occurred with possible formation of a Schiff base such as is described below (E).

Procedure E. 4-Dimethylamino-4′-(4-dimethylaminobenzylidineamino)chalcone $[(p)(CH_3)_2$-$NC_6H_4CH{=}CHCOC_6H_4N{=}CHC_6H_4N(CH_3)_2(p)]$. The synthesis was patterned after that of 4′-benzylidineaminochalcone (25).

Sodium hydroxide (100 ml.; 10%) was added to a stirred suspension of 13.5 g. of 4-aminoacetophenone and 30 g. of 4-dimethylaminobenzaldehyde in 200 ml. of methanol (38–40° for ten minutes); cooling and filtering gave 18 g. of orange-colored solid; m.p. 164–168°. Recrystallizations were from a butanone-ethanol mixture and from pyridine.

(4-Acetylphenyl)urea (26) was prepared in a new way by adding 100 g. of aluminum chloride under stirring and cooling to a mixture of 40 g. of phenylurea, 500 ml. of carbon disulfide, and 35 g. of acetyl chloride (15–20° for four hours); it was recrystallized from hot water; 16 g. (31%).

Ethyl 4-acetylcarbanilate (26) was prepared by a somewhat modified procedure, as follows: 32.4 g. of ethyl chloroformate was added to a stirred suspension of 40.5 g. of 4-aminoacetophenone in 800 ml. of ether followed by a solution of 12 g. of sodium hydroxide in 100 ml. of water. As the temperature rose from 20° to 30° a precipitate appeared. After cooling for thirty minutes and allowing to stand overnight at room temperature with consequent evaporation of solvent, 54 g. (70%) was obtained, m.p. 155–157°; recrystallized from benzene, m.p. 158–159°.

3-(4-Dimethylaminophenyl)-1-phenyl-2-propen-1-ol [$(p)(CH_3)_2NC_6H_4CH{=}CHCHOHC_6H_5$]. A mixture of 25.1 g. (0.1 mole) of 4-dimethylaminochalcone (27) and 200 ml. of 1.5 *N* aluminum isopropoxide was heated for three hours under partial reflux with distillation of most of the solvent. Hydrolysis with dilute sodium hydroxide, extraction with ether, concentration, and crystallization from *n*-heptane gave 9 g. (36%); m.p. 92–95°; two additional crystallizations and one more from isopropanol gave slightly yellow plates; m.p. 99–100°.

Anal. Calc'd for $C_{17}H_{19}NO$: C, 80.59; H, 7.56.

Found: C, 80.60; H, 7.58.

This compound, like other styrylmethanols (28), forms intensely colored solutions in dilute hydrochloric acid, but no crystalline product could then be recovered.

Nuclear-substituted benzalacetophenone (chalcone) dibromides. The new chalcone dibromides used in the synthesis of the dimorpholinyl ketones (listed in Table III) were made by dropwise addition of the calculated amount of bromine to a stirred solution of the chalcone in chloroform or carbon tetrachloride as solvent. Cooling, or evaporation in the case of the more soluble compounds, gave the dibromides in good yields.

THE COMPOUNDS MADE FROM BENZALPINACOLONE

1-tert.-Butyl-2,3-dimorpholinyl-3-phenyl-1-propanone (VI). Benzalpinacolone (29) was brominated in chloroform; yield 91%, m.p. 124–125°. A suspension of 44.8 g. of the *dibromide* in 150 ml. of ethanol was treated with 43.6 g. of morpholine (two hours under stirring); the resulting crystalline precipitate was filtered and washed with water; 17.7 g. (38.5%); m.p. 190.5–191.5°. It crystallized as pale yellow needles from ethanol; m.p. 194°.

Anal. Calc'd for $C_{21}H_{32}N_2O_3$: C, 69.97; H, 8.95.

Found: C, 69.93; H, 9.04.

THE (4-HALOGENOBENZAL)ACETONE SERIES

(4-Chlorobenzal)acetone (30). Attempts to make this compound by the directions of Walther and Raetze (30), or by the standard procedure for benzalacetone (31), were unsuccessful. The following scheme was developed. A solution of 0.3 g. of sodium hydroxide in 170 ml. of ethanol, 40 ml. of acetone, and 230 ml. of water, was added dropwise to a solution of 10 g. of *p*-chlorobenzaldehyde in 60 ml. of ethanol over one hour under stirring. Yellow crystals began separating. After twelve hours of continued stirring, the solid was filtered; 3.5 g. (32%); m.p. 150–180°. Recrystallization from benzene gave pure bis-(4-chlorobenzal)-acetone; m.p. 193–194°;

Anal. Calc'd for $C_{17}H_{12}Cl_2O$: C, 67.34; H, 3.99.

Found: C, 67.27; H, 4.10.

The filtrate from the above, upon concentrating and diluting with water, gave 8.2 g. (64%) of product (m.p. 50–54°). Crystallization from ligroin gave needles, m.p. 59–59.5° [W. and R. (30) reported 50–51°].

Anal. Calc'd for $C_{10}H_9ClO$: C, 66.49; H, 5.02.

Found: C, 66.17; H, 5.10.

4-(4-Chlorophenyl)-3,4-dimorpholinylbutanone-2 (VIIb) (SN 8335). The dibromide of 4-(chlorobenzal)acetone [$ClC_6H_4CHBrCHBrCOCH_3$] was prepared by bromination in

carbon tetrachloride at room temperature (standing for nine hours), evaporation of the solvent, and crystallization from ligroin (yield 50%; m.p. 78–79.5°). A solution of 14 g. of the dibromide in 65 ml. of absolute ethanol was treated with 14.4 g. of morpholine. After fifteen minutes the precipitated morpholine hydrobromide was filtered (92%) and the filtrate on concentration gave a solid which was washed with, and then crystallized from, methanol; yield 6.3 g. (46%); m.p. 128.5–129°.

Anal. Calc'd for $C_{18}H_{25}ClN_2O_3$: N, 7.94.
Found: N, 7.71.

1-(4-Chlorophenyl)-5-(N,N-benzylmethylamino)-1-penten-3-one hydrobromide (XVI). A mixture of 5 g. of paraformaldehyde, 33 g. of benzylmethylamine hydrobromide, two drops of conc'd hydrobromic acid, 125 ml. of dry benzene, and 29.5 g. of 4-chlorobenzalacetone was refluxed for two hours and allowed to stand overnight (the calculated amount of water which was evolved was collected with a calibrated trap under the reflux condenser). Cooling gave 56.7 g.; recrystallization from absolute ethanol gave 37 g. (57%); m.p. 144–147°.

Anal. Calc'd for $C_{19}H_{20}ClNO \cdot HBr$: N, 3.55.
Found: N, 3.34.

1-(4-Chlorophenyl)-5-morpholinyl-1-penten-3-one hydrochloride, made as above, was precipitated by ether (yield 90%); recrystallized from 97% ethanol, m.p. 195–198°.

Anal. Calc'd for $C_{15}H_{18}ClNO_2 \cdot HCl$: Cl^-, 11.21.
Found: Cl^-, 11.46.

The *dibromide* of this [$ClC_6H_4CHBrCHBrCOCH_2CH_2NC_4H_8O \cdot HCl$] was made by dropwise addition of bromine to a cooled carbon tetrachloride solution of the above, over one hour. The crystalline precipitate was recrystallized from methanol; m.p. 156–157°.

Anal. Calc'd for $C_{15}H_{18}Br_2ClNO_2 \cdot HCl$: Cl^-, 7.45.
Found: Cl^-, 7.61.

Bis-(4-bromobenzal)acetone [$BrC_6H_4CH{=}CHCOCH{=}CHC_6H_4Br$]. The following procedure was designed to attain optimum yield of the mono-(4-bromobenzal) compound. A solution of 19.5 g. of *p*-bromobenzaldehyde in 112 ml. of ethanol was added over six hours under stirring to a solution of 0.6 g. of sodium hydroxide in 80.5 ml. of acetone, 340 ml. of ethanol, and 460 ml. of water. A yellow solid separated. After stirring for an additional six hours and acidification with conc'd acetic acid, the precipitate was filtered; 8 g. (39%). It was crystallized thrice from benzene; yellow, m.p. 211–211.5°.

Anal. Calc'd for $C_{17}H_{12}Br_2O$: Br, 40.76.
Found: Br, 40.77.

(4-Bromobenzal)acetone [$BrC_6H_4CH{=}CHCOCH_3$]. The filtrate from the crude bis-(4-bromobenzal) compound (above) was concentrated under reduced pressure and diluted with water. The precipitate (12.5 g.; 37%) was crystallized from ligroin (charcoal); m.p. 83–84°.

Anal. Calc'd for $C_{10}H_9BrO$: C, 53.35; H, 4.03.
Found: C, 53.48; H, 4.15.

The *dibromide* [$BrC_6H_4CHBrCHBrCOCH_3$] was made by dropwise addition of bromine in carbon tetrachloride to the 4-bromobenzal compound in this solvent. The yield of nearly pure product after crystallization from ligroin, was 65%. Further purification by recrystallization (charcoal) gave m.p. 104–104.5°.

Anal. Calc'd for $C_{10}H_9Br_3O$: C, 31.20; H, 2.36.
Found: C, 31.11; H, 2.40.

5-Morpholinyl-1-phenyl-1-penten-3-one hydrobromide was made in the usual way by the Mannich reaction from benzalacetone (in absolute ethanol, refluxing for five hours); recrystallized from absolute ethanol, m.p. 180–181°.

Anal. Calc'd for $C_{15}H_{19}NO_2 \cdot HBr$: N, 4.29. Found: N, 4.07.

4-(4-Bromophenyl)-3,4-dimorpholinyl-2-butanone (VIIc). A mixture of 15 g. of the dibromide (above), 75 ml. of absolute ethanol, and 15 g. of morpholine, after standing for twenty-four hours, was filtered to remove morpholine hydrobromide (11.8 g.) and evaporated. The residue, which solidified, was washed with and recrystallized from methanol; 3.2 g., m.p. 169–170°.

Anal. Calc'd for $C_{18}H_{25}BrN_2O_3$: N, 7.05. Found: N, 6.80.

1-(4-Bromophenyl)-5-(N,N-benzylmethylamino)-1-penten-3-one hydrobromide (XVI) was made like the 4-chloro analog, but under three hours of refluxing. The product was precipitated by addition of dry ether and recrystallized from absolute ethanol, yield 44%; crystallized thrice from absolute ethanol, m.p. 154–155°.

Anal. Calc'd for $C_{19}H_{20}BrNO \cdot HBr$: N, 3.15. Found: N, 3.09.

THE 4-CHLORO- AND 4-BROMO-α,β-DIMORPHOLINYLPROPIOPHENONES

α,β-Dibromo-4-chloropropiophenone (IX). A solution of 50 g. (0.2 mole) of α,β-dibromopropionyl chloride (VIII) in 30 ml. of carbon disulfide was added over one hour to a stirred mixture of 22.5 g. (0.2 mole) of chlorobenzene, 33.4 g. (0.25 mole) of anhydrous aluminum chloride, and 100 ml. of carbon disulfide, and the mixture was refluxed for 15 min. Hydrolysis with ice and hydrochloric acid, extraction with ether, washing, and evaporation gave a solid residue which was crystallized from ethanol; 55.5 g. (85%); m.p. 56–57°. Recrystallization thrice from ethanol gave m.p. 57–58°.

Anal. Calc'd for $C_9H_7Br_2ClO$: C, 33.11; H, 2.16.
Found: C, 33.42; H, 2.50.

4-Chloro-α,β-dimorpholinylpropiophenone (Xa). Morpholine (45 g.) was added slowly over thirty minutes to a cooled solution of 30 g. of XVII in 100 ml. of acetone. The mixture, after refluxing for one hour and standing at room temperature for four hours, was filtered and evaporated. The residual oil was washed; it ultimately crystallized, and washing with petroleum ether gave 3.8 g. (76%). It was recrystallized twice from ethanol (charcoal), m.p. 96–97°.

Anal. Calc'd for $C_{17}H_{23}ClN_2O_3$: N, 8.27. Found: N, 8.05.

4-Chloro-α,β-bis-(2-methyl-4-morpholinyl)propiophenone was prepared like Xa (above) except that absolute ether was used as the solvent, and crystallizations were from butanone; m.p. 154–155°. The 2-methylmorpholine (11) was furnished by Dr. W. S. Cottle.

Anal. Calc'd for $C_{19}H_{27}ClN_2O_3$: N, 7.64. Found: N, 7.86.

α,β,4-Tribromopropiophenone (13) was prepared by adding 60 g. (0.24 mole) of VIII over one hour to 36 g. (0.24 mole) of bromobenzene and 35 g. of anhydrous aluminum chloride in 400 ml. of carbon disulfide at 5°, and allowing the mixture to stand for twelve hours at room temperature. Crystallization of the product from ethanol gave 70 g. (78%). Three crystallizations from ethanol (once with charcoal) gave a pure sample; m.p. 56–57°. Kohler's product (13) obtained under different reaction conditions melted at 74° and may be either a stereoisomer or a different crystalline form.

Anal. Calc'd for $C_9H_7Br_3O$: C, 29.14; H, 1.90.
Found: C, 29.32; H, 2.00.

4-Bromo-α,β-dimorpholinylpropiophenone (Xb) (SN 6551). A solution of 30 g. of XVII in 150 ml. of absolute ether at 0° was treated with 29 g. of morpholine, and was filtered after three hours standing. Evaporation, washing, and crystallization from methanol gave 22.5 g. (73%). Three crystallizations from methanol, once with charcoal, gave m.p. 101.5–102°.

Anal. Calc'd for $C_{17}H_{23}BrN_2O_3$: C, 53.28; H, 6.05.
Found: C, 53.50; H, 6.15.

α,β-DIMORPHOLINYL KETONES CONTAINING A NAPHTHALENE RING

α,β-Dimorpholinyl-β-phenyl-1-propionaphthone (XI). Benzaldehyde (37 g.; 0.35 mole) was added fairly rapidly to a stirred mixture of 59.8 g. (0.35 mole) of methyl 1-naphthyl ketone, 18 g. of sodium hydroxide, 100 ml. of ethanol, and 160 ml. of water (cooled during the addition), and stirring was continued for eighteen hours. The yellow oil, *benzal-1-acetonaphthone* (not analyzed) was extracted with ether and this solution was treated dropwise with 56 g. (0.35 mole) of bromine with short heating initially to start the reaction. After stirring for two hours the solid *dibromide* was filtered; 118 g. (81%); m.p. 165–171° (not analyzed). A suspension of 17.7 g. of the dibromide in 100 ml. of absolute ethanol and 17.4 g. of morpholine was refluxed for thirty minutes, cooled and filtered, and the solid residue washed with water; yield 11.4 g. (66%); m.p. 185–189°. Recrystallization from ethyl acetate gave colorless needles; m.p. 202°.

Anal. Calc'd for $C_{27}H_{30}N_2O_3$: C, 75.32; H, 7.02.
Found: C, 75.52; H, 7.36.

β-Phenyl-α,β-bis(1,2,3,4-tetrahydro-2-isoquinolyl)-1-propionaphthone was made similarly in 81% yield from the above dibromide in acetone medium (mixture shaken for fifteen minutes); crystallized from ethanol-chloroform mixture; light yellow needles; yield 26%; m.p. 176–177°.

Anal. Calc'd for $C_{37}H_{36}N_2O$: N, 5.34. Found: N, 5.15.

α-Morpholinyl-β-phenyl-1-acrylonaphthone (XIII). A suspension of 16.7 g. of the above dibromide in 100 ml. of absolute ethanol was treated with 20 ml. of methanol containing one equivalent (0.9 g.) of dissolved sodium, and was allowed to stand overnight. The resulting *mono-bromo* compound (not isolated) was treated with 3.9 g. of morpholine under cooling and the mixture was allowed to stand for 1½ hours at room temperature. The suspension of the solid *α-bromo-β-morpholinyl compound* (not characterized) was treated with a solution of 1.4 g. of sodium in 20 ml. of methanol (stirring for 15 min.). Cooling and filtering gave 10.5 g. (76%); recrystallized from ethanol, yellow, m.p. 116°.

Anal. Calc'd for $C_{23}H_{21}NO_2$: N, 4.08. Found: N, 4.22.

β-Phenyl-2-acrylonaphthone [$C_6H_5CH{=}CHCOC_{10}H_7(\beta)$]. A mixture of 59.8 g. of methyl 2-naphthyl ketone, 18 g. of sodium hydroxide, 150 ml. of ethanol, 100 ml. of water, and 37.1 g. (0.35 mole) of benzaldehyde, cooled initially, was allowed to stand for 45 min., and the precipitate (88.3 g.; 98%) was recrystallized from ethanol; diamond-shaped plates; m.p. 105°.

Anal. Calc'd for $C_{19}H_{14}O$: C, 88.34; H, 5.46.
Found: C, 88.41; H, 5.52.

The *dibromide* was made by dropwise addition of bromine to a cooled chloroform solution and subsequent addition of ether and cooling; the precipitate (61%) was recrystallized from ethyl acetate and ethanol; thick needles; m.p. 175°.

Anal. Calc'd for $C_{19}H_{14}Br_2O$: C, 54.58; H, 3.38.
Found: C, 54.92; H, 3.21.

α,β-Dimorpholinyl-β-phenyl-2-propionaphthone was prepared in 62% yield according to procedure A (above); it crystallized as needles from ethanol; m.p. 165.5–167°.

Anal. Calc'd for $C_{27}H_{30}N_2O_3$: C, 75.32; H, 7.02.
Found: C, 75.53; H, 6.80.

α,β-Dibromo-β-1-naphthylpropiophenone [$(\alpha)C_{10}H_7CHBrCHBrCOC_6H_5$]. α-Naphthaldehyde (31.2 g.) was added under stirring to a cooled mixture of 24 g. of acetophenone, 200 ml. of ethanol, and 100 ml. of 10% sodium hydroxide, cooled initially and allowed to stand at room temperature for two hours. The oil, *β-1-naphthylacrylophenone* (not characterized) was extracted with ether and brominated by dropwise addition of 28.8 g. of bromine. The precipitate, and a second crop obtained from concentration of the solution, was 53.7 g. (64%); it crystallized from ethyl acetate as square plates; m.p. 176°.

Anal. Calc'd for $C_{19}H_{14}Br_2O$: C, 53.58; H, 3.38.
Found: C, 54.69; H, 3.47.

α,β-Dimorpholinyl-β-1-naphthylpropiophenone (XII). The mixture obtained according to Procedure A (above) seemed, from the analysis, to consist of a mixture of the desired compound and the α-morpholinyl unsaturated ketone. No attempt was made to work up and to isolate the latter. The mixture was recrystallized from ethanol (by dilution with water) and from a 3:1 ethanol-ethyl acetate mixture; pale yellow needles; m.p. 161°.

Anal. Calc'd for $C_{27}H_{30}N_2O_3$: N, 6.51. Found: N, 6.67.

COMPOUNDS MADE FROM DIBENZALACETONE

5-Morpholinyl-1,5-diphenyl-1-penten-3-one (XV) was prepared by the action of 26 g. (0.3 mole) of morpholine in 250 ml. of dry ether on 23.4 g. (0.1 mole) of dibenzalacetone (8.5 hours). The resulting white precipitate was filtered; 28.5 g. (90%); m.p. 134–136°; recrystallized from ethyl acetate, m.p. 142.5–144°.

Anal. Calc'd for $C_{21}H_{23}NO_2$: N, 4.36. Found: N, 4.46.

When heated in 60% ethanol it was converted back into dibenzalacetone with loss of morpholine. Attempts to get the dimorpholine addition compound failed.

TABLE IV

ANALYSES

COMPOUND NO. (TABLES I-III)	CRYSTALLIZED FROM[a]	EMPIRICAL FORMULA	CARBON (OR NITROGEN = N)		HYDROGEN	
			Calc'd	Found	Calc'd	Found
1	Ethanol	$C_{24}H_{30}N_2O_3$	7.10	7.24	—	—
2	IsoPr.	$C_{26}H_{34}N_2O_3$	N6.63	6.32	—	—
3	Abs. EtOH	$C_{27}H_{36}N_2O_3$	N6.42	6.61	—	—
4	EtOH-EtOAc	$C_{29}H_{38}N_2O_3$	N6.06	6.04	—	—
5	Ethanol	$C_{31}H_{36}N_2O_3$	76.83	76.57	7.46	7.51
			N5.78	5.81	—	—
6	Acet. EtOH	$C_{29}H_{32}N_2O_3$	N6.14	6.10	—	—
7	Ligroin	$C_{23}H_{27}ClN_2O_3$	N6.75	7.08	—	—
8	Ethanol	$C_{23}H_{27}BrN_2O_3$	N6.10	5.78	—	—
9	Methanol	$C_{23}H_{27}N_3O_5$	64.92	65.05	6.40	6.55
			N9.88	9.92	—	—
10	Abs. EtOH	$C_{25}H_{31}N_3O_4$	68.31	68.02	7.14	6.97
			N9.60	9.69	—	—
11	Hept. tol.	$C_{26}H_{33}N_3O_5$	N8.99	9.02	—	—
12	Ethanol	$C_{24}H_{30}N_2O_4$	N6.83	6.62	—	—
13	Ethanol	$C_{25}H_{32}N_2O_4$	N6.60	6.75	—	—
14	Ethanol	$C_{26}H_{34}N_2O_4$	N6.39	6.48	—	—
15	Ethanol	$C_{26}H_{34}N_2O_4$	N6.39	6.34	—	—
16	Abs. EtOH	$C_{27}H_{36}N_2O_4$	71.65	71.41	7.84	8.35
			N6.19	6.10	—	—
17	Benz. ligr	$C_{29}H_{32}N_2O_4$	N5.93	6.38	—	—
18	Methanol	$C_{26}H_{34}N_2O_4$	N6.39	6.68	—	—
19	Methanol	$C_{23}H_{27}ClN_2O_3$	N6.75	6.57	—	—
20	Ethanol	$C_{24}H_{30}N_2O_3$	73.07	73.25	7.67	8.08
21	Ethanol	$C_{23}H_{27}N_3O_5$	64.92	64.73	6.40	6.67
22	Ethanol	$C_{24}H_{30}N_2O_4$	70.22	69.93	7.37	7.51
23	Ethanol	$C_{25}H_{32}N_2O_3$	N6.86	6.76	—	—
24	Ethanol	$C_{29}H_{40}N_2O_3$	N6.03	5.85	—	—
25	Ethanol	$C_{23}H_{26}Cl_2N_2O_3$	N6.24	6.22	—	—
26	Ethanol	$C_{25}H_{31}BrN_2O_5$	57.81	58.42	6.02	6.10
			N5.39	5.08	—	—
27	Ethanol	$C_{25}H_{32}N_2O_5$	N6.36	6.12	—	—
28	Ethanol	$C_{24}H_{29}ClN_2O_3$	N6.53	6.71	—	—
29	Lig. EtOAc	$C_{27}H_{36}N_2O_4$	N6.19	6.04	—	—
30	Ethanol	$C_{26}H_{34}N_2O_3$	N6.63	6.88	—	—
31	Ethanol	$C_{27}H_{36}N_2O$	N6.93	7.12	—	—
32	Ethanol	$C_{27}H_{36}N_2O$	N6.93	7.24	—	—
33	Ethanol	$C_{26}H_{34}N_2O_2$	76.81	76.78	8.43	8.23
			N6.89	6.72	—	—
34	Ethanol	$C_{31}H_{36}N_2O_2$	N5.99	6.03	—	—
35	EtOH-CHCl$_3$	$C_{34}H_{34}N_2O_2$	N5.57	5.48	—	—
36	Methanol	$C_{29}H_{28}N_2O$	N6.66	6.95	—	—
37	Ethanol	$C_{27}H_{30}N_2O_2$	78.23	78.32	7.30	7.62
38	Methanol	$C_{30}H_{30}N_2O$	N6.45	6.53	—	—
39	Acetone	$C_{25}H_{26}N_2O_2$	N7.25	7.41	—	—
40	Methanol	$C_{26}H_{28}N_2O_2$	N7.00	7.06	—	—

TABLE IV—*Concluded*

COMPOUND NO. (TABLES I-III)	CRYSTALLIZED FROM[a]	EMPIRICAL FORMULA	CARBON (OR NITROGEN = N) Calc'd	CARBON (OR NITROGEN = N) Found	HYDROGEN Calc'd	HYDROGEN Found
42	Hexane	$C_{25}H_{23}NO_2$	81.27	80.87	6.28	6.46
			N3.79	3.84	—	—
43	Methanol	$C_{19}H_{18}ClNO_2$	N4.27	4.06	—	—
44	Hexane	$C_{19}H_{18}BrNO_2$	61.30	61.04	4.87	4.67
			N3.76	4.03	—	—
45	Heptane	$C_{19}H_{18}N_2O_4$	N8.28	8.10	—	—
46	EtOAc-pet.	$C_{20}H_{21}NO$	82.43	82.27	7.26	7.48

CPD. NO.	EMPIRICAL FORMULA	ANALYSIS C (or N) Calc'd	ANALYSIS C (or N) Found	ANALYSIS H Calc'd	ANALYSIS H Found	CPD. NO.	ANALYSIS C (or N) Calc'd	ANALYSIS C (or N) Found	ANALYSIS H Calc'd	ANALYSIS H Found
49	$C_{21}H_{22}O$	86.85	86.65	7.64	7.48	68	52.96	52.95	4.46	4.55
50	$C_{23}H_{20}O$	88.42	87.81	6.45	6.33	69	53.80	53.92	4.75	4.79
51	$C_{17}H_{15}NO_2$	N5.28	5.29	—	—	71	58.49	58.32	4.27	4.79
52	$C_{18}H_{17}NO_3$	N4.74	4.74	—	—	72	56.78	57.05	3.63	3.73
53	$C_{16}H_{14}N_2O_2$	N10.52	10.54	—	—	73	44.76	44.48	2.75	2.81
54	$C_{18}H_{18}O_2$	81.17	80.93	6.81	6.50	74	48.02	47.76	3.56	3.45
							N3.30	3.28	—	—
55	$C_{18}H_{18}O_2$	81.17	81.41	6.81	7.07	75	47.50	47.71	3.76	3.66
57	$C_{19}H_{21}NO_2$	N5.02	5.00	—	—	76	50.73	51.00	4.26	4.08
58	$C_{17}H_{16}O$	86.40	86.38	6.83	6.71	77	50.73	50.77	4.26	4.49
59	$C_{15}H_{10}Cl_2O$	64.77	64.95	3.64	3.79	78	51.84	51.44	4.58	4.53
60	$C_{16}H_{13}ClO$	74.85	74.62	5.10	4.96	79	50.30	50.32	3.69	3.80
61	$C_{19}H_{20}O_2$	81.40	81.64	7.19	7.51	80	48.27	48.41	3.54	3.19
62	$C_{19}H_{20}N_2O_2$	N9.09	9.48	—	—	81	51.41	51.72	4.06	3.96
63	$C_{21}H_{24}N_2O_2$	N8.33	8.52	—	—	82	55.77	55.62	5.35	5.36
64	$C_{20}H_{22}N_2O_3$	N8.28	8.56	—	—	83	41.22	41.12	2.31	2.69
65	$C_{22}H_{26}N_2O_3$	72.10	71.56	7.15	7.12	84	47.27	46.12	3.22	3.31
		N7.65	7.83	—	—					
66	$C_{18}H_{19}N_3O_2$	N13.58	13.83	—	—	85	51.84	51.68	4.58	4.69
67	$C_{26}H_{27}N_3O$	78.55	78.52	6.85	6.97	86	47.69	47.24	3.77	3.55

[a] Solvent abbreviations: isoPr. = isopropanol; EtOAc = ethyl acetate; acet. = acetone; hept. = heptane; tol. = toluene; benz. = benzene; ligr. = ligroin; pet. = petroleum ether.

1,5-Diphenyl-5-piperidyl-1-penten-3-one was prepared similarly by the action of piperidine on dibenzalacetone in ligroin (12 hours), yield 78%; repeated recrystallizations from ligroin gave m.p. 91–92°.

Anal. Calc'd for $C_{22}H_{25}NO$: N, 4.39. Found: N, 4.30.

Attempts to obtain the dipiperidyl addition compound indicated that it was formed to some extent but was unstable, and it was not isolated pure.

Attempts to add dibutylamine to dibenzalacetone failed.

Catalytic reduction of dibenzalacetone (32) to dibenzylacetone was accomplished effectively by means of Raney nickel in 95% ethanol at atmospheric pressure (three hours).

2,4-Dibromo-1,5-diphenylpentan-3-one. Dibromination of dibenzylacetone (above) was effected in absolute ether. The reaction mixture was cooled after initiating the reaction with

a few drops of bromine. After washing the solution with water and evaporating, the residue was fractionally crystallized from ligroin. The first fraction (55%) was *isomer-A;* m.p. 96–99°; recrystallization from ligroin gave m.p. 100.5–101°.

Anal. Calc'd for $C_{17}H_{16}Br_2O$: Br, 40.25. Found: Br, 40.92.

The second crop was a mixture of isomers. The filtrate on evaporation gave a 6% yield of material of m.p. 63.5–65°, *isomer-B*, which after repeated crystallizations from isopropanol had m.p. 64.5–65°.

Anal. Calc'd for $C_{17}H_{16}Br_2O$: Br, 40.25. Found: Br, 39.98.

2,4-Dimorpholinyl-1,5-diphenylpentan-3-one (XIV) was made by adding morpholine dropwise to an ether solution of either of the isomeric dibromo ketones (above) and allowing the mixture to stand overnight at room temperature. A 56% yield was obtained in the case of *isomer-A* by crystallization of the products from isopropanol; m.p. 120–121°.

Anal. Calc'd for $C_{25}H_{32}N_2O_3$: N, 6.86. Found: N, 6.41.

SUMMARY

α,β-Dimorpholinyl-β-phenylpropiophenone was found to be one-tenth as active as quinine against avian malaria. Derivatives have been made with various nuclear substituents, including alkyl, phenyl, halogen, alkoxyl, nitro, acetamido, and carbethoxyamino, and many of these show similar antimalarial activity. The synthesis of these compounds has involved the preparation of a number of new chalcones and their dibromides, and some related α-morpholinyl chalcones. Absorption spectra of six of the substituted chalcones are reported.

New preparations of β-morpholinyl and β-piperidyl chalcones are described.

α,β-Dimorpholinyl ketones were made from the following: benzalpinacolone, *p*-chloro- and *p*-bromo-benzalacetones, *p*-chloro- and *p*-bromo-phenyl vinyl ketones, benzal-1 (and -2) -acetonaphthones, and α-naphthalacetophenone.

α,α'-Dimorpholinyldibenzylacetone is described. Attempts to make the β,β'-analog from dibenzalacetone gave only the mono-morpholine addition product.

Some new Mannich reaction products from *p*-chloro- and *p*-bromo-benzalacetone are described.

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[Contribution from the Department of Chemistry and Chemical Engineering of the University of Pennsylvania]

THE COURSE OF THE MANNICH REACTION[1]

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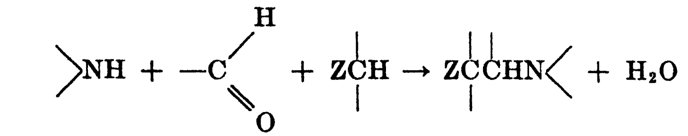
The Mannich reaction (1) may be represented in generalized form:



I II III XI

in which I is a primary or secondary amine or ammonia, II is usually formaldehyde, though other aldehydes have been used (2), and III is a compound containing activated hydrogen on carbon (1, 3, 4, 5); similar condensations may occur when activated hydrogen is on nitrogen (6). The course of the reaction has proved elusive. Bodendorf and Koralewski (7) tested experimentally the hypothesis that the initial step is the condensation of formaldehyde (II) with either I or III to yield $ZCCH_2OH$ (V) or $—NCH_2OH$ (VI), but concluded that neither hydroxymethyl compound satisfies fully the requirements of an intermediate. The suggestion of Cromwell (8) that in alcohol solution the intermediate may be the ether of VI, and the discussion of the manner of interaction of nitroparaffins, formaldehyde, and amines, by Johnson (2d), led to no tested conclusion of sufficient scope to account for the Mannich reaction.

The view that methylene-*bis*-amine (VII) may serve as intermediate has not been suggested hitherto but is entirely plausible. Feldman and Wagner (6) obtained Mannich bases by interaction of phenols with methylene-*bis*-amines, as well as with amines and formaldehyde. Methylene-*bis*-amines can form under the usual conditions of the Mannich reaction. An accumulation of evidence showing that in presence of acid methylene-*bis*-amines (VII) participate in reactions involving the grouping $RNCH_2—$ led to the conclusion (9) that in acid-induced reactions an alkylidene-*bis*-amine may accept a proton to form a salt (such salts are known) which by loss of amine leaves a carbenium ion $RNCH_2^+$. The same ion is obtainable from VI in analogous manner (with elimination of water), and also from a Schiff base by addition of proton (9). These preliminary operations are shown in Figure 1. The assumption that these condensation products may yield a common ion is consistent with the observation that all three

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can be used interchangeably in certain reactions which involve the grouping $\mathrm{R}\overset{|}{\mathrm{N}}\mathrm{CH_2}$—. In view of the fact that this grouping is formed during the Mannich reaction, it seemed desirable to test experimentally the hypothesis that the methylene-*bis*-amine is eligible to function as intermediate. Its eligibility was established by successful use of methylene-*bis*-amines in abbreviated Mannich reactions. There were used in this way the methylene-*bis*-amines of piperidine, morpholine, and dibenzylamine. As reactant III there were used acetophenone, antipyrine, β-naphthol, dibenzoylmethane, and dimethyldihydroresorcinol (methone). For comparison, ordinary Mannich reactions were run with formaldehyde, amine, and the same compound of type III. In all cases the two procedures yielded the same products and, for similarly favorable conditions, in approximately the same amounts (Tables I and II). The reactions thus realized with VII and III, and with I, II, and III, yielded the following normal Mannich products: β-piperidinopropiophenone, 4-piperidinomethylantipyrine, 4-dibenzylaminomethylantipyrine, 4-morpholinomethylantipyrine, 1-dibenzylaminomethylnaphthol-2, and 1-morpholinomethylnaphthol-2; Feldman and Wagner (6) obtained analogous Mannich bases from naphthol-1 and naphthol-2 and carvacrol, using the methylene-*bis*-amines from piperidine, *p*-toluidine, and *p*-chloroaniline. When III was dibenzoylmethane or methone both dibenzylamine or morpholine with formaldehyde and their methylene-*bis*-amines yielded not the Mannich bases but secondary compounds of familiar types, *viz.*, 1,1,3,3-tetrabenzoylpropane and methylene-*bis*-methone. It is interesting to note that 1,1,3,3-tetrabenzoylpropane was obtained by Wesenberg (11) from dibenzoylmethane and formaldehyde, but only in the presence of piperidine or dimethylamine as "catalyst", and that Desai (12) found piperidine to catalyze condensations of aldehydes with methone. These are presumed to be Mannich reactions each followed by elimination of amine in a further condensation to yield a bimolecular methylene compound; although proof of an intermediate Mannich base is lacking, these reactions respond to alkaline and acidic catalysis in much the same manner as other Mannich reactions. The Knoevenagel reaction, when catalyzed by primary or secondary amines, may follow a similar course. Several of the reactions of methylene-*bis*-amines were realized under rigorously anhydrous conditions, and were therefore not due to formaldehyde produced hydrolytically from VII by small amounts of water operating cyclically. The hydroxymethyl amine (VI), probably the primary product of condensation of amine and aldehyde, was shown by Bodendorf and Koralewski (7) to give subnormal yields of Mannich products. It is easily converted to methylene-*bis*-amine except in presence of excess of aldehyde (10). Since, as shown later, excess of aldehyde does not promote the Mannich reaction (when conditions otherwise are favorable), a preference for VII as the active intermediate is justified, though because of a result discussed later VI cannot be entirely excluded.

That these reactions of methylene-*bis*-amines or hydroxymethyl amines are induced by proton attack and may involve ion X is inferable from the fact that

under mild conditions they occur only in presence of some acidic compound,[3] which may be hydrochloric acid, or III, or even ammonium chloride.[4] The existence of ion X cannot be demonstrated experimentally, but assumption of such an intermediate has permitted rationalization of a number of superficially diverse acid-induced reactions of aldehydes with primary or secondary amines, or of corresponding methylene-*bis*-amines or Schiff bases previously studied in this laboratory (6, 13, 14, 15).

Compound III is in some degree acidic and is the source of ion IV which finally unites with ion X to form the Mannich base. If III is frankly acidic (*e.g.*, a phenol) it can participate in Mannich reactions under mild conditions and in absence of added acid (6) or even in presence of alkali in small amount (4).

The simultaneous formation of cation X and of anion IV requires, or may be subject to, a dual catalysis in an amphoteric system. This is possible during a Mannich reaction, for one reactant is a base and one is in some degree an acid, and added acid (if not more than equivalent to the amine) is not free, but throughout the reaction is combined more or less completely with amine I, with any basic intermediates, and with the Mannich base. Compound III, when sufficiently acidic, may induce reaction in absence of added acid, and conversely the basic components of the mixture may promote formation of ion IV. The acid-base relationships suitable for individual Mannich reactions can be associated qualitatively with differences in the acid characters of compounds of type III and in the basic characters of the amines used. Optimum initial acid-base relationships thus established semi-empirically may not persist throughout the reaction but may change progressively as I and III are consumed in formation of the Mannich base. Experimental results support this view, for with favorable acid-base relationships Mannich reactions gave good yields in relatively short periods, but when conditions were initially less favorable, or became so, reactions were slow and yields low in the same periods of time, though improved if reaction periods were considerably extended. This effect of time is consistent with the reaction course suggested, for in it the Mannich base is represented as a terminal compound. The view that decrease in reaction rate is due to depletion of the mixture with respect to a primary reactant is represented by the common practice of

[3] Reaction of methylene-*bis*-amine can be forced in absence of acid by operation at higher temperature; antipyrine and methylene-*bis*-dibenzylamine at 150–160° and in absence of added acid formed 4-(dibenzylaminomethyl)antipyrine in high yield (Table II). The thermally induced reaction may involve either the radical R_2NCH_2— or thermal dissociation of antipyrine as an acid. Methylene-*bis*-amines of the type $ArNHCH_2NHAr$ are thermally cleaved in part during distillation (17), forming some amine and Schiff base which appears as trimer. Compounds of the type $R_2NCH_2NR_2$ cannot undergo similar cleavage into isolable products, but in presence of compounds with reactive hydrogen, and capable of involvement with the cleavage fragments R_2N and CH_2NR_2, thermally induced reactions may yield the same products as do acid-induced reactions (9).

[4] The effectiveness of ammonium chloride at room temperature is slight, but at somewhat elevated temperatures its influence may be marked (Table I). A slow evolution of ammonia from the predominantly basic reaction mixture suggests that the action of ammonium chloride is not specific but is due to hydrogen chloride.

introducing additional formaldehyde during the reaction period. Since under favorable conditions the best yields were obtained when reactants were taken in equivalent quantities, it seems that decrease in reaction rate is not a merely statistical effect but is a result of deteriorating acid-base relationships, which interfere by obstructing the condensation of amine and aldehyde.

The acid-base relationships in the Mannich reaction, hitherto neglected, seem to be essential to an understanding of the process. They constitute in each case a controllable variable which affects the rapidity and degree of completeness of the reaction, and this view is capable of experimental testing. Reactions leading to ion X require presence of acid in at least catalytic amount, but amine-aldehyde condensations are impeded by excess acid,[5] which will operate also to depress formation of ion IV. It follows that for each set of reactants there should be some optimum concentration of acid and also some concentration above which the formation of Mannich base will be impeded or checked. This was verified experimentally for the reactions of antipyrine, naphthol-2, and dibenzoylmethane with formaldehyde and the amines morpholine and dibenzylamine (Table I), which were progressively slowed and in most cases finally inhibited by increasing amounts of acid. The effect of added alkali upon condensation of amine and aldehyde is not obstructive (17), but alkali sufficient to depolarize most of the protons present will check formation of ion X and prevent the Mannich reaction, even though formation of IV is favored. This also was verified experimentally for the reactants named (Table I). It is believed that these experimental results afford significant support for the proposed reaction course which made them predictable.

Retention of the hydroxymethyl amine (VI) as a possible intermediate seems advisable because in absence of added acid addition of formaldehyde to a mixture of antipyrine and dibenzylamine led to formation of methylene-*bis*-dibenzylamine and a small amount of the Mannich base, though methylene-*bis*-dibenzylamine and antipyrine failed to react, and no reaction occurred when antipyrine was added to a mixture of dibenzylamine and formaldehyde. In the first case a little Mannich base was obtained by a path other than *via* the methylene-*bis*-amine (here inoperative in absence of acid stronger than antipyrine), and this may involve compound VI, though hydroxymethyldibenzylamine is a compound thus far not reported [*cf.*(10)].

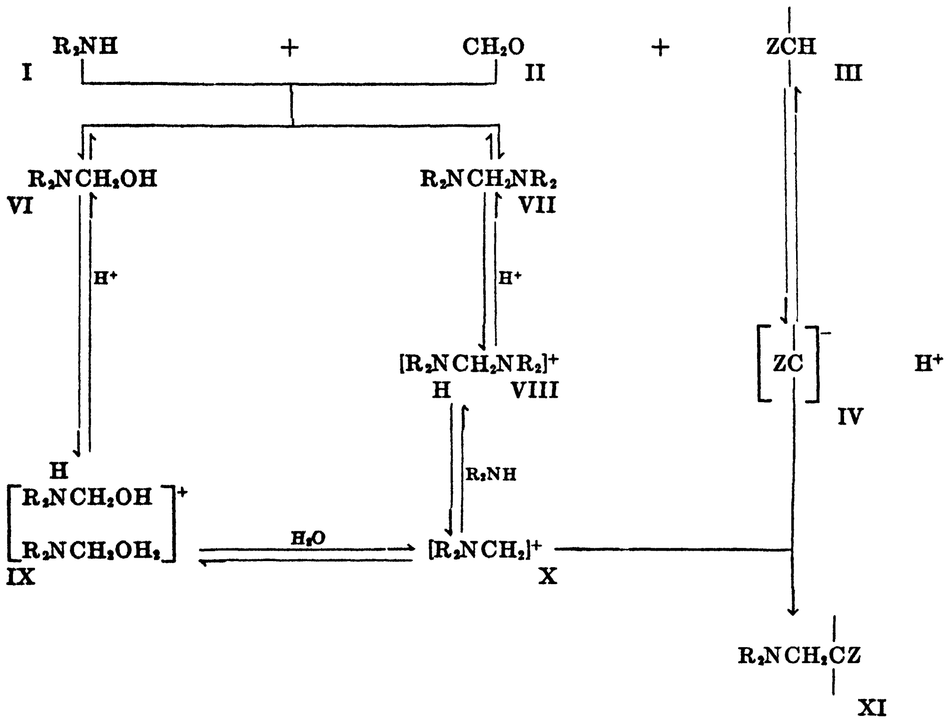
The final step in the reaction (union of polar fragments IV and X) is probably substantially irreversible, but this cannot be asserted dogmatically in view of the reversibility of certain carbon-carbon condensations such as those leading to diacetone alcohol,[6] aldols, etc. The carbon-carbon bonds established in the

[5] Methylene-*bis*-arylamines, and also Schiff bases derived from arylamines, may not persist owing to secondary reactions.

[6] Mannich bases of the type $\mathrm{RNH\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}C{\scriptstyle(=O)R}}$, retaining a reactive hydrogen, are nitrogen system analogs of diacetone alcohol and may form reversibly.

Mannich reactions studied appear to be resistant to cleavage, but the carbon-nitrogen bonds could be cleaved. When 1-(dibenzylaminomethyl)naphthol-2 was heated with morpholine the product was 1-(morpholinomethyl)naphthol-2; when the latter was heated with dibenzoylmethane the morpholine unit was displaced, yielding 1-(2,2-dibenzoylethyl)naphthol-2. The use of Mannich bases for alkylations involves similar exchanges, which may be attributed to carbenium ions (X) or to a direct replacement mechanism, the latter suggested by Snyder

FIGURE 1. THE COURSE OF THE MANNICH REACTION[a]



[a] Representation of I as a secondary amine and II as formaldehyde are restrictions imposed for simplicity. If I is a primary amine, the initial condensation product may be the Schiff base $RN{=}CH_2$, which by addition of H^+ may yield X (9).

and Eliel (16). The course of the Mannich reaction, derived as explained above, is shown in Figure 1.

Experiments to test the rate of interaction of antipyrine, morpholine, and formaldehyde under uniform conditions led to yields determined with insufficient accuracy to permit estimation of rate or the order of the reaction, but it is clear that with reactants in equivalent amounts the rate is initially high and decreases rapidly, though reaction may continue during a considerable further period. The optimum acid-base relationships in any case, and the advisability or admissibility of adding acid or alkali, depend upon the basic character of I and the acidic character of III. The results reported point to the conclusions (a) that with in-

creasing basicity of I the favorable influence of acid, and the amount that may be added profitably, decreases and that of alkali increases, (b) that with increasing acidity of III the favorable influence of acid decreases and that of alkali increases, and (c) that Mannich reactions which require considerable initial acidity may give maximum yields in reasonable periods only if a compensatory increase in the amount of an initial reactant is made during or at the outset of the reaction, or if the concentration of acid is progressively decreased by neutralization as reaction proceeds.

EXPERIMENTAL

Melting points reported are corrected values. Elementary analyses were performed by Sarah M. Woods. New compounds are designated by asterisk*. Constants for chemicals used, and references for their preparations, are as follows: Morpholine and piperidine, fractions of b.p. 127–128° and 105–105.5°, respectively; dibenzoylmethane (18), m.p. 77–78°; methylene-*bis*-piperidine (6) and methylene-*bis*-morpholine (9), b.p. 78–79° (1 mm.) and 136° (20 mm.), respectively; methylene-*bis*-dibenzylamine (19) after crystallization melted at 97–98°, a value slightly low, so identity was confirmed by analysis: Calc'd: C, 85.8; H, 7.38; Found: C, 85.8; H, 7.32.

MANNICH REACTIONS. GENERAL PROCEDURES AND EXPERIMENTAL TRIALS

Preparations of piperidinopropiophenone (20) and 4-(piperidinomethyl)antipyrine (21) under usual conditions gave yields of 86% and 66%, but the nature of the isolations did not qualify these reactions for the semiquantitative experiments planned. The examples studied are outlined below. In experiments designed to test the catalytic effects of added acid or alkali the conditions selected for the comparison experiments were such as to give relatively low yields in reactions without added catalyst.

**1-(Dibenzylaminomethyl)naphthol-2*. A solution of 7.2 g. of naphthol-2, 9.85 g. of dibenzylamine in 75 ml. ethanol, and 4.0 ml. of 35% formalin (added last; all reactants 0.05 mole) was heated under reflux for an hour, then chilled; yield 15.8 g. (90%), m.p. 117–117.5° (cryst. from ethanol).

Anal. Calc'd for $C_{25}H_{23}NO$: C, 85.0; H, 6.51; N, 3.97.
Found: C, 85.0; H, 6.40; N, 3.77.

The same compound was obtained from naphthol-2 (1.44 g.; 0.01 mole) and methylene-*bis*-dibenzylamine (4.06 g.; 0.01 mole) by similar treatment; yield 3.0 g. (86%), m.p. 116.5–117°.

**1-(Morpholinomethyl)naphthol-2*. Solutions of 1.44 g. of naphthol-2, 0.9 ml. of morpholine, and 0.8 ml. of formalin (added last; all reactants 0.01 mole) in 25 ml. of 95% ethanol were allowed to stand at room temperature; upon chilling the solution the product crystallized. Reaction periods and yields: 30 min., 49%; 60 min., 74%; 180 min., 82%. After crystallization from ethanol the compound melted at 114.5–115°.

Anal. Calc'd for $C_{15}H_{17}NO_2$: C, 74.1; H, 7.05.
Found: C, 74.0; H, 7.20.

Experiments in the presence of added hydrochloric acid or sodium hydroxide yielded the results included in Table I; these products all melted in the range 113.5–114.5°. The same compound was obtained from naphthol-2 (1.44 g.; 0.01 mole) and methylene-*bis*-morpholine (1.9 g.; 0.1 mole) by similar treatment; yield 1.0 g. (41%), m.p. 112.5–114°. An experiment under anhydrous conditions gave a yield of 39%. The effects of added hydrochloric acid or sodium hydroxide are shown in Table II.

**4-(Dibenzylaminomethyl)antipyrine*. A solution of 1.97 g. of dibenzylamine, 1.88 g. of antipyrine, and 0.8 ml. of formalin (added last; all reactants 0.01 mole) in 20 ml. of ethanol

TABLE I

INFLUENCE OF ACID, BASE, TIME, TEMPERATURE ON YIELDS BY MANNICH REACTION

REACTANTS, SOLVENTS	CATALYST (EQUIV.)			TIME, HRS	TEMP.	YIELD, %
	HCl[a]	NH_4Cl	NaOH[b]			
Naphthol-2, dibenzylamine, HCHO[c] (1:1:1) in 95% ethanol	0	0	0	1	reflux	90[d]
Naphthol-2, morpholine, HCHO (1:1:1) in 95% ethanol	2.0			3	room	0
	1.0			3	"	50[e]
	0.1			3	"	74
	.05			1	"	72
	.01			0.5	"	49
	0	0	0	.5	"	49
	0	0	0	1.0	"	74
	0	0	0	3.0	"	82
			0.01	0.5	"	57
			.05	1	"	71
			.1	3	"	70
			1.0	3	"	30
			2.0	3	"	0
Antipyrine, dibenzylamine, HCHO (1:1:1) in 95% ethanol	1			2	reflux	0
		0.01		2	"	89[f]
	0	0	0	2	"	12
			0.1	2	"	0
			1.0	2	"	0
Antipyrine, morpholine, HCHO (1:1:1) in water	5			24	room	4[g, h]
	3			24	"	17
	2			24	"	42
	1			24	"	72
	0.1			24	"	76
	.01			24	"	48
	0	0	0	24	"	41
			.01	24	"	43
			.1	24	"	44
			1	24	"	36
			5	24	"	11[h]
Dibenzoylmethane, dibenzylamine, HCHO (1:1:1) in ethanol	2			2	reflux	0
	1			2	"	100[i, j]
		0.4		2	room	50
		.2		2	"	45
		.1		2	"	40
		.1		2	reflux	81
		.05		2	room	29, 37
	0	0	0	2	"	37
	0	0	0	18	"	78
	0	0	0	2	reflux	86
			0.05	2	room	81
			.05	18	"	77
			1.4	18	"	0

TABLE I—*Concluded*

REACTANTS, SOLVENTS	CATALYST (EQUIV.)			TIME, HRS.	TEMP.	YIELD, %
	HCl[a]	NH$_4$Cl	NaOH[b]			
Dibenzoylmethane, morpholine, HCHO (1:1:1) in 95% ethanol	1[k]			2	room	0
	0.1			2	"	28[j]
	.05			2	"	31
	0	0	0	2	"	30
			0.1	2	"	76
			1.0	2	"	0

[a] HCl taken as 0.447 *N* or conc'd HCl.[b] NaOH taken as 4% aqueous sol.[c] Formaldehyde taken as 35% formalin in all experiments.[d] Product is 1-(dibenzylaminomethyl) naphthol-2.[e] Product is 1-(morpholinomethyl)naphthol-2.[f] Product is 4-(dibenzylaminomethyl) antipyrine.[g] Product is 4-(morpholinomethyl)antipyrine.[h] This small yield probably due to reaction during isolation procedure following neutralization.[i] Crude product.[j] Product is 1,1,3,3-tetrabenzoylpropane.[k] Morpholine used as hydrochloride.

was heated under reflux for 2 hours. Hot water was added to incipient turbidity and the mixture was chilled, causing separation of some methylene-*bis*-dibenzylamine. The filtrate was concentrated to about 10 ml., hot water was added to faint turbidity, and the mixture was chilled overnight, yielding 0.5 g. (12%) of dibenzylaminomethylantipyrine, m.p. 122–125°. In the presence of 0.1 equiv. of ammonium chloride the same reactants yielded 3.53 g. (89%) of product, m.p. 126.5–128.5°. During the heating, ammonia was detected in the vapors. Recrystallization from ethanol yielded pure 4-(dibenzylaminomethyl)antipyrine, m.p. 131–132°.

Anal. Calc'd for $C_{26}H_{27}N_3O$: C, 78.6; H, 6.80; N, 10.6.
Found: C, 78.5; H, 6.82; N, 10.5.

By use of dibenzylamine hydrochloride (1 equiv. of acid) with antipyrine and formalin no Mannich base was obtained; the isolated materials were 64% of dibenzylamine hydrochloride and a 74% yield of methylene-*bis*-antipyrine of m.p. 153–154° (22). Antipyrine, dibenzylamine, and formalin in presence of 0.1 equiv. of sodium hydroxide yielded no Mannich base but 80% of methylene-*bis*-dibenzylamine. In presence of 1 equiv. of sodium hydroxide the mixture yielded no solid product. The sensitivity of this reaction to added acid or base is noteworthy; a good yield is obtained only in presence of a small amount of acid (Table I).

4-(Dibenzylaminomethyl)antipyrine was obtained similarly from methylene-*bis*-dibenzylamine (4.06 g., 0.01 mole), antipyrine (1.88 g., 0.01 mole), and ammonium chloride (0.05 g., 0.001 mole) in 20 ml. of ethanol. After heating the mixture for two hours, addition of hot water to turbidity, and chilling, there separated 3.35 g. (84%) of product, m.p. 124–127°. A reaction attempted in absence of ammonium chloride produced no Mannich base, and 96% of the methylene-*bis*-dibenzylamine was recovered.

Reaction under anhydrous conditions. Into a dried flask provided with a reflux condenser and calcium chloride tube, and containing 1.88 g. (0.01 mole) of antipyrine, 4.06 g. (0.01 mole) of methylene-*bis*-dibenzylamine, and 0.3 g. (0.001 mole) of dibenzylamine hydrochloride, there was distilled about 25 ml. of anhydrous ethanol directly from a mixture with sodium ethoxide and diethyl phthalate. After heating under reflux for two hours the mixture was cooled, seeded, and kept overnight in a refrigerator. The product (2.8 g., 70%) melted at 124–128°, and after recrystallization from ethanol, at 131–132°.

A reaction without added catalyst was thermally forced by heating in a sealed tube at 150–160° for 3 hours a mixture of 0.005 mole each of methylene-*bis*-dibenzylamine (2.0 g.)

and antipyrine (0.94 g.). The chilled liquid yielded 1.05 g. (53%) of Mannich base (m.p. 128–130°), and a second crop of 0.68 g. (34%, m.p. 118–124°) was obtained from the filtrate.

4-(Morpholinomethyl)antipyrine. A solution of 1.88 g. of antipyrine and 0.87 g. of morpholine in 20 ml. of water, and with or without added acid or alkali as indicated in Table I, was treated with 0.8 ml. of formalin (all reactants 0.01 mole). After 24 hours at room tempera-

TABLE II

MANNICH REACTIONS WITH METHYLENE-*bis*-AMINES

REACTANTS, SOLVENTS	CATALYST (EQUIV.)			TIME, HRS.	TEMP.	YIELD, %
	HCl	NH_4Cl	NaOH			
Napthol-2, methylene-*bis*-dibenzylamine, (1:1) in 95% ethanol	0	0	0	1	reflux	86[a]
Naphthol-2, methylene-*bis*-morpholine (1:1) in 95% ethanol	0.05			1	room	58[b]
	0	0	0	1	"	41
			0.05	1	"	29
Antipyrine, methylene-*bis*-dibenzylamine (1:1) in 95% ethanol		0.1		2	reflux	84[c]
	0	0	0	2	"	0
	0	0	0	3	150–160°	87[d]
Antipyrine, methylene-*bis*-morpholine (1:1) in water	0.1			24	room	22[e]
	.01			24	"	52
	0	0	0	24	"	48
			0.1	24	"	5, 14[f]
			5	24	"	23[f]
Dibenzoylmethane, methylene-*bis*-dibenzylamine (1:1) in ethanol	0	0	0	2	room	28[g]
	0	0	0	2	reflux	88
		0.1		2	room	27
		.1		2	reflux	93
Dibenzoylmethane, methylene-*bis*-morpholine (1:1) in ethanol	0	0	0	2	room	28[g]
	0.1			2	"	32
			0.1	2	"	65

[a] Product identified as 1-(dibenzylaminomethyl)naphthol-2.[b] Product identified as 1-(morpholinomethyl) naphthol-2.[c] Product identified as 4-(dibenzylaminomethyl)antipyrine.[d] Thermally induced reaction.[e] Product identified as 4-(morpholinomethyl) antipyrine.[f] This small yield probably due to reaction during isolation procedure following neutralization.[g] Product identified as 1,1,3,3-tetrabenzoylpropane.

ture the mixture was treated with 2 ml. of conc'd hydrochloric acid and any surviving antipyrine was removed by three 10-ml. extractions with chloroform. The aqueous liquid was made alkaline (40% aqueous sodium hydroxide) and 4-(morpholinomethyl)antipyrine was extracted in three 10-ml. portions of chloroform. The combined extracts were dried over potassium carbonate, the solvent was removed under reduced pressure, and the residue was crystallized from 15–20 ml. of ethyl acetate. The products obtained in eleven experiments (Table I) under varied conditions all melted between 128.5° and 130.5°; the m.p. reported for 4-(morpholinomethyl)antipyrine is 131° (23). The fact that a large excess of either acid

or alkali failed to prevent formation of Mannich base, and also the relatively low sensitivity to changes in acid or alkali, may be attributed to incidental reaction during the isolation procedure when, owing to necessary neutralizations, conditions more favorable than those set for the reaction were temporarily operative.

4-(Morpholinomethyl)antipyrine was obtained also from methylene-*bis*-morpholine and antipyrine as recorded in Table II.

Time-yield experiments. A solution of 18.8 g. (0.1 mole) of antipyrine, 8.7 g. (0.1 mole) of morpholine, and 22 ml. of 0.447 *N* hydrochloric acid (0.01 mole, the optimum amount; see Table I) in 200 ml. of water in a 250-ml. volumetric flask was cooled in an ice-bath, and 8.0 ml. of 35% formalin (0.1 mole of formaldehyde) was added rapidly. The volume was made up to 250 ml. and the flask was placed in a constant temperature bath at 25 ± 0.1°. At intervals 25-ml. aliquots were removed and Mannich base was isolated as outlined above. A uniform procedure was used for these operations and for crystallization from 20 ml. of ethyl acetate. The results of two such experiments are as follows:

Time, min.	20	30	40	60	80	120	160	180	320	360	24 hr.
Exp. 1 Yield, %	—	29	—	31	—	37	—	43	—	59	70
Exp. 2 " "	26	—	32	—	41	—	44	—	54	—	—

1,1,3,3-Tetrabenzoylpropane was obtained as the sole product when dibenzoylmethane was used as compound III with formaldehyde and either dibenzylamine or morpholine. In experiments with dibenzylamine, reactions at room temperature were incomplete in 2 hours, and in 18 hours approached the maximum, which was reached in 2 hours when the mixture was heated under reflux. The product separated when the mixture was chilled. When reactions were incomplete more or less methylene-*bis*-dibenzylamine was present. This was removed by warming the mixture for several minutes with ethanol containing hydrochloric acid (1 conc'd HCl: 40 EtOH). Upon chilling the solution the nearly pure product (m.p. 171–175°) separated. After crystallization from ethanol it was pure, m.p. 175.5–176°. Since this was not the expected product its identity as tetrabenzoylpropane (11) was corroborated by analysis.

Anal. Calc'd for $C_{31}H_{24}O_4$: C, 80.8; H, 5.25;
Found: C, 80.8; H, 5.15.

Results obtained without catalyst and in the presence of varying amounts of acid, ammonium chloride or alkali appear in Table I. This reaction was inhibited by excess of acid or alkali, but otherwise was more affected by temperature than by identity or amount of catalyst, suggesting that tetrabenzoylpropane may not be formed *via* the Mannich base, though the persistence of methylene-*bis*-dibenzylamine in incomplete reactions suggests the reverse. In similar experiments with morpholine (Table I) reaction at room temperature was promoted by 0.1 equiv. of alkali, and was inhibited by excess of either acid or alkali, the effects of catalysts resembling those in the Mannich reactions studied, suggesting a course *via* the Mannich base. Tetrabenzoylpropane was obtained also by interaction of methylene-*bis*-dibenzylamine or methylene-*bis*-morpholine with dibenzoylmethane in equivalent amounts (Table II).

Methylene-bis-methone. Methone (0.7 g., 0.005 mole) and 0.0025 mole of methylene-*bis*-amine (0.45 g. of methylene-*bis*-piperidine, 1.01 g. of methylene-*bis*-dibenzylamine, or 0.47 g. of methylene-*bis*-morpholine) in 10 ml. of 50% ethanol reacted at 100° to yield in 5 minutes 0.5–0.6 g. of methylene-*bis*-methone, which separated upon chilling the solution; m.p. 191–191.5° (12b).

Transposition reactions. 1. Conversion of 1-(dibenzylaminomethyl)naphthol-2 (3.53 g., 0.01 mole) to 1-(morpholinomethyl)naphthol-2 was effected by heating the former with 0.9 ml. (0.01 mole) of morpholine in 20 ml. of 95% ethanol for seven hours under reflux; the product (1.8 g., 77%) separated upon chilling the mixture. The m.p. 105–109° was raised to 113.5–114° by two recrystallizations from ethanol. A mixture with an authentic specimen of

1-(morpholinomethyl)naphthol-2 had the same m.p. 2. Conversion of 1-(morpholinomethyl)naphthol-2 (1.21 g., 0.005 mole) to *1-(2,2-dibenzoylethyl)naphthol-2 was effected by heating the former with dibenzoylmethane (1.12 g., 0.005 mole) in 25 ml. of 95% ethanol in the presence of 0.6 ml. of 0.45 *N* hydrochloric acid for two hours under reflux. On chilling the mixture the crude product (1.0 g., 53%; m.p. 103–109°) separated slowly. Recrystallization from ethanol yielded the pure compound, m.p. 121–121.5°.

Anal. Calc'd for $C_{26}H_{20}O_3$: C, 81.8; H, 5.30.

Found: C, 81.9; H, 5.27.

SUMMARY

The Mannich reaction is believed to involve a dual catalysis in an amphoteric system in which the cation $R_2N\overset{|}{\underset{|}{C}}{}^+$ is formed from the condensation product(s) of amine and carbonyl compound, and combines finally with the anion of the reactive-hydrogen compound. Formation of the cation is induced by added acid or by the acidity of the reactive-hydrogen compound or both. Formation of the anion is promoted by the bases present or by added alkali or both. The inferences that excessive acid would interfere with the primary condensation of amine and carbonyl compound and would depress the ionization tendency of the reactive-hydrogen compound, and that excessive alkali would decrease or prevent formation of the cation $R_2N\overset{|}{\underset{|}{C}}{}^+$, and therefore would obstruct or stop the reaction, were supported experimentally. The probability that the cation originates in the alkylidene-*bis*-amine formed from aldehyde and amine was strengthened by demonstration that methylene-*bis*-amines, used instead of aldehydes and amines, produced normal yields. A suggested reaction scheme which incorporates these views appears to be consistent with available evidence.

PHILADELPHIA 4, PENNA.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF CALIFORNIA]

AZABICYCLOALKANES. 2-AZABICYCLO[3·3·1]NONANE[1,2]

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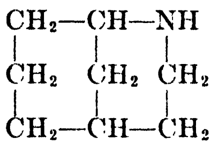
Although a large number of compounds bearing certain structural relationships to morphine have been synthesized and tested for analgesic activity (1) no study has yet been made of derivatives of the simple bicyclic N-bridge system (I) postulated for the Gulland and Robinson morphine formula (2). Recently Grewe (1b, 3) has synthesized an analgesically active compound (II) containing the entire morphine skeleton with the exception of the oxygen bridge, and Schnider and Grüssner (4), using Grewe's method, have made the 3-hydroxy



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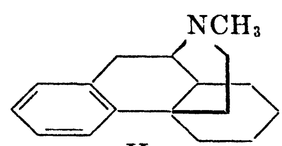


II

derivative. Horning (5) has prepared a tetralin-piperidine structure with a bicyclic N-bridge and phenolic hydroxyls corresponding to those in positions 3 and 4 of morphine. Barltrop (6) has made two quaternary salts containing the fused system.

Attempted syntheses of the unsubstituted (I) itself have not proved fruitful (7)[4] and it was felt that if convenient methods of synthesis could be developed for the simple azabicyclononanes, further work of a similar nature with slightly more complex structures might lead to pharmacologically interesting derivatives.

The fact that Ferber and Bruckner (8) were able to prepare 2-azabicyclo-[2·2·2]octane by copper chromite reduction of the lactam of *cis*-4-aminocyclohexanecarboxylic acid suggested that the unsubstituted 2-azabicyclo[3·3·1]nonane (I) could be synthesized in an analogous fashion by lactamization of *cis*-3-aminocyclohexaneacetic acid and subsequent catalytic reduction of the resulting lactam. When *m*-nitrobenzaldehyde was treated with benzoyl chloride and sodium cyanide according to the procedure of Francis and Davis (9) *m*-nitro-O-benzoylmandelonitrile (III) was obtained in good yield. Alcoholic hydrogen chloride converted the nitrile into the ester (IV) which was hydrogenated in

[1] Presented before the Division of Organic Chemistry, American Chemical Society, Chicago, Illinois, April 22, 1948.

[2] Robinson and Barltrop have suggested the trivial name "morphan" for this ring system (6).

[3] American Chemical Society Post-Doctoral Fellow, University of California, Berkeley, 1946–1948.

[4] Protiva and Sorm, *Collection Czechoslov. Chem. Communs.*, **13**, 428 (1948); *Chem. Abstr.*, **43**, 1730 (1949), started the preparation of this lactam by way of cyclohexanone-3-acetic acid→oxime→amino acid but did not proceed further after receiving the preliminary report (footnote 1) of this work; M. Protiva, private communication.

ethanol over Raney nickel and sodium carbonate at 120° to give the ethyl ester of *m*-aminophenylacetic acid in an over-all yield from *m*-nitrobenzaldehyde of 69% for the three-step process. If sodium hydroxide, sodium bicarbonate, or N,N′-diethylcyclohexylamine were used in place of the sodium carbonate to react with the benzoic acid produced by the hydrogenolysis the reaction was slow and incomplete even at 150°.[5]

Previously mandelic nitriles, acids, esters, and O-acyl nitriles and esters have been reduced over platinum or palladium (11) and ethyl mandelate has been reduced over Raney nickel (12).

Three different methods were used for the preparation of the lactam (VI) of *cis*-3-aminocyclohexaneacetic acid. The first method followed the procedure used by others (8, 13) for the reduction of an amino acid containing an aromatic amino group to its corresponding hexahydro derivative. The hydrochloride of ethyl *m*-aminophenylacetate was hydrogenated over platinum at 60–70° in ethanol to give a mixture of the *cis* and *trans* hexahydro esters (V) in the ratio of about 3:7. By heating this mixture at 200° in ethanol the *cis* ester was converted into the lactam (VI) and a majority of the *trans* ester was recovered unchanged.

The second method of preparation made use of the hydrogenation of the sodium salt of *m*-aminophenylacetic acid over Raney nickel at 200° in a *tert*-butyl alcohol-water mixture. The reduction was unsatisfactory when carried out in either the alcohol or water alone. Heating the amino acids so obtained at 250° gave the desired lactam in a yield which indicated a *cis*-*trans* ratio of 5:1. The free *m*-nitrophenylacetic acid reduced under the same conditions gave a 20% yield of the lactam (VI). The ethyl ester gave only unchanged starting material and tar.

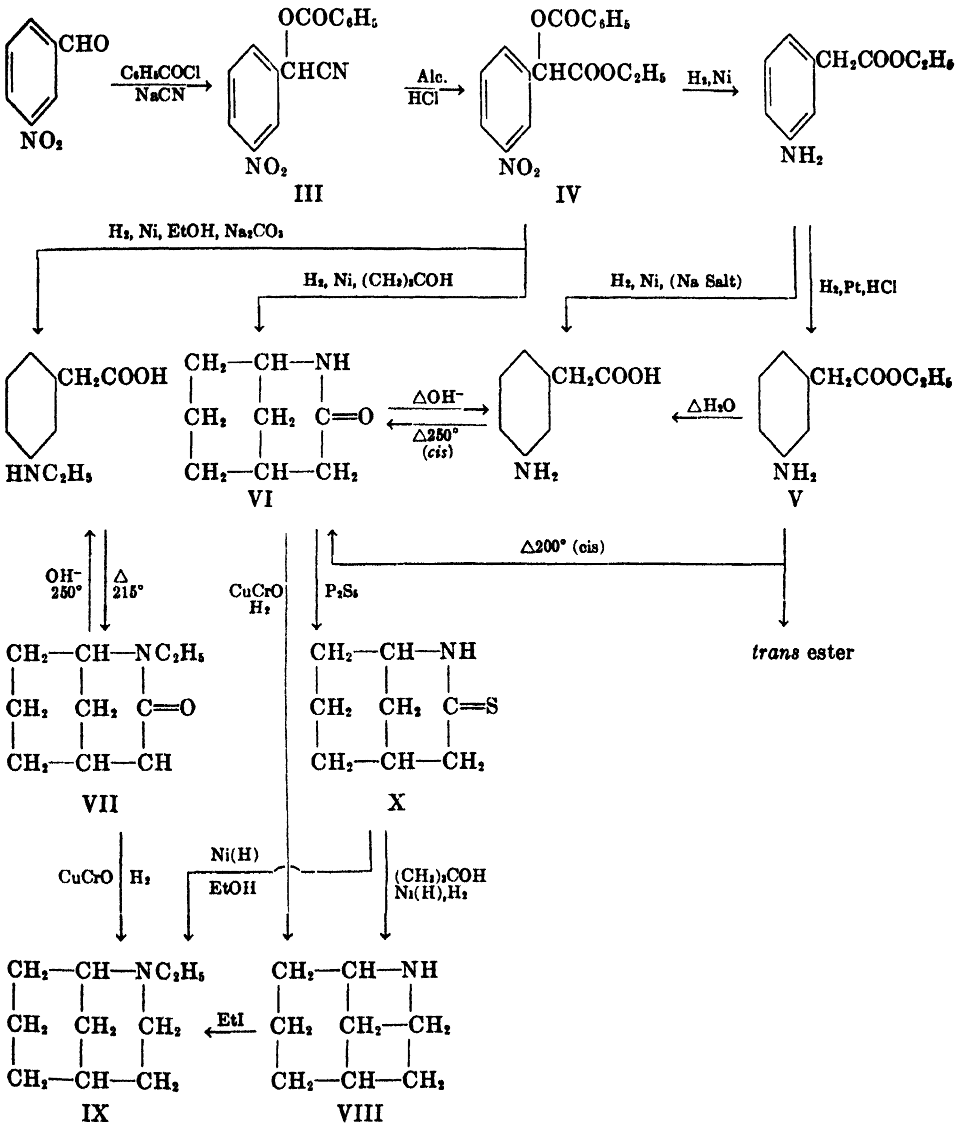
The third and most useful method for the synthesis of the lactam was the direct hydrogenation over Raney nickel of the ethyl ester of *m*-nitro-O-benzoylmandelic acid (IV) in *tert*-butyl alcohol at 200°. After a number of runs under a variety of conditions the optimum yields obtainable were 32–36%. When *m*-nitro-O-benzoylmandelic acid was hydrogenated as the sodium salt under the same conditions the yield of lactam was less than 10%. When one or two equivalents of sodium bicarbonate or sodium carbonate were added in the reduction of the ester (IV) the yields were 10–20% and *m*-nitromandelic acid alone gave only a 10% yield. The rate of hydrogen uptake seemed to indicate that the O-benzoyl group was removed more rapidly and at a lower temperature than the free hydroxyl and that the hydrogenolysis occurred more satisfactorily with the ester than with the free acid or its sodium salt.

tert-*B*utyl alcohol was chosen as the solvent for these hydrogenations when it was found that it could be used directly without special purification, that it did not alkylate the amino group (14), and that it was apparently stable over Raney nickel up to 220°. It has been used over copper chromite up to 260°.[6]

[5] The apparently increased activity of Raney nickel in the presence of sodium carbonate has been noted in other cases (10).

[6] The maximum useable temperatures were not determined.

Ethyl *m*-nitro-O-benzoylmandelate (IV) hydrogenated over Raney nickel in ethanol at 180° gave a mixture of the two lactams (VI) and VII) and the ethyl ester of N,N'-diethyl-3-aminocyclohexaneacetic acid. However, when two moles



of sodium carbonate were added so that the hydrogenation proceeded first (120°) to ethyl *m*-aminophenylacetate and then through the sodium salt, the principal product was N-ethyl-*cis*-3-aminocyclohexaneacetic acid which was heated at 215° and lactamized to (VII) in an over-all yield of 27–32%.

The two lactams (VI) and (VII) were hydrogenated to their respective amines

(VIII) and (IX) over copper chromite in *tert*-butyl alcohol. The 2-azabicyclo[3·3·1]nonane (VIII) was apparently unstable over copper chromite under the conditions necessary for hydrogenation since the yield was 30% with 16% recovery of starting lactam after three hours at 220° and 20% with no recovery after six hours. The same decrease of yield with increased time of contact was also observed at 200° and 250°. The N-ethyl lactam (VII), on the other hand, required a temperature of 250° for any appreciable reduction and the resulting amine (IX) was more stable and was obtainable in higher yield. For comparison 2-ethyl-2-azabicyclo[3·3·1]nonane (IX) was also made by the reaction of (VIII) with ethyl iodide.

As a variation the lactam (VI) was converted into the thiolactam (X) by means of phosphorus pentasulfide. In order to convert thiolactams to cyclic amines Ruzicka (15) used an electrolytic method;[7] however, it has been found that this reduction could also be accomplished by refluxing the thiolactam with Raney nickel in an alcohol solvent. Although a number of different types of compounds have been desulfurized in this fashion (16) the procedure has not been applied previously to thiolactams.

When the thiolactam was refluxed with Raney nickel in absolute ethanol the product was the N-ethyl derivative (IX).[8] The alkylation of amines by alcohols has been studied extensively at 150–200° (17) but apparently the method has not been used at lower temperatures; although it has been observed that aniline was alkylated by ethanol during the reduction of nitrobenzene under similar conditions (18). A sample of the secondary amine (VIII) was alkylated to (IX) under hydrogen, thus demonstrating that the process is actually one of direct alkylation rather than the possible reductive alkylation via the acetaldehyde which may be generated by refluxing the ethanol solution open to the air or in contact with a hydrogen acceptor such as the aldimine form —CH=N— (19).

The secondary amine (VIII) was obtained in 64% yield by heating the thiolactam with Raney nickel in *tert*-butyl alcohol under a positive pressure of hydrogen. Refluxing the thiolactam with the catalyst in *tert*-butyl alcohol gave incomplete reduction and a mixture of products similar to that which was obtained with the less active nickel in ethanol.[8]

The two lactams showed differences in the ease with which they could be hydrolyzed. Sixty per cent of the lactam (VI) was recovered after refluxing with 10% sodium hydroxide for twenty-four hours and 80% was unchanged after twenty-four hours with concentrated hydrochloric acid at 160° in a sealed tube. It was finally hydrolyzed to the extent of at least 90% after six hours at 210° in 1 *N* sodium hydroxide. The N-ethyl lactam (VII) at 220° for twelve hours in 1 *N* sodium hydroxide gave 65% unreacted starting material. Even after fifteen hours at 250° in 2 *N* sodium hydroxide 27% was recovered unchanged.

The azabicycloalkanes described in this work have been tested for possible

[7] Ruzicka (23) has recently applied $LiAlH_4$ to lactam reduction and obtained 60–95% yields of the polymethylene imines.

[8] In early experiments a less active catalyst than that described by Adkins and Pavlic (20) was used. The results have not been clarified as yet since the products seemed to be a mixture of (IX) and the aldimine —CH=N— or its trimer.

analgesic activity under the direction of Dr. Nathan B. Eddy, National Institutes of Health, Bethesda, Maryland. The lactams (VI) and (VII) exhibit definite analgesic activity, which appears quickly and is brief. Both are convulsant. The amines (VIII) and (IX) were toxic and inactive.

EXPERIMENTAL

All melting points are corrected. Microanalyses were performed by C. W. Koch and V. H. Tashinian.

m-Nitro-O-benzoylmandelonitrile (III). To a well-stirred suspension of 302 g. (2 moles) of *m*-nitrobenzaldehyde (Eastman) in 400 ml. of water in a 4-liter beaker cooled to 0–5° in an ice-bath there was added, in one portion, 245 ml. (2.05 moles) of benzoyl chloride. After a few seconds for mixing, a solution of 118 g. (2.2 moles) of 95% sodium cyanide in 250 ml. of water was added all at once. Within a few seconds the temperature rose to 80° and then dropped to 50–60° at which time crystallization set in. The solid was filtered, washed with water, and air dried. One crystallization from ethanol gave 495 g. (88%) of product; m.p. 98–101°. A sample recrystallized from alcohol formed colorless leaflets; m.p. 99.5–101°.

Anal. Calc'd for $C_{17}H_{15}N_2O_6$: C, 63.81, H, 3.57; N, 9.92.

Found: C, 64.05; H, 3.75; N, 9.95.

Ethyl m-nitro-O-benzoylmandelate (IV). To a solution of 200 g. of dry hydrogen chloride in 1200 ml. of absolute ethanol there was added 564 g. (2.0 moles) of the nitrile (III). The solution was heated to refluxing and there was added 50 ml. of water in several portions with swirling. The mixture was refluxed for thirty minutes and was filtered hot. The ester crystallized from the filtrate and was thoroughly washed with water and air dried to give 562 g., m.p. 76–79°; a second crop was recrystallized from ethanol to give 32 g., m.p. 75–79° (yield 90%). A sample was recrystallized from absolute ethanol; small prisms, m.p. 78.5–80.0°.

Anal. Calc'd for $C_{10}H_{13}NO_2$: C, 62.00; H, 4 59; N, 4.25.

Found: C, 61.90; H, 4.48; N, 4.56.

Ethyl m-aminophenylacetate. A suspension of 165 g. (0.5 mole) of the mandelic ester (IV), 53 g. of sodium carbonate (0.5 mole), and 25 g. of Raney nickel (20)[9, 10] in 300 ml. of absolute

[9] The method of preparation of the nickel seemed to have no discernable effect on the yield, and catalyst which had stood for six months was no less effective than the fresh material.

[10] During the course of this work some rather interesting observations were made concerning the effects exerted by the stainless steel liners sometimes used for catalytic hydrogenations. The optimum conditions for the three different Raney nickel hydrogenations starting with the ester (VI) had been worked out with several score reactions on a 0.05-mole scale in bomb sizes of 180 to 300 ml. capacities without a liner. When the reactions were scaled up to the 0.5- mole size larger bombs with stainless steel liners were used. The results, at first attributed simply to the increased size of the run, varied from 10% less yield than expected down to nothing at all. Furthermore, the nature of the products had changed. A majority of the hexahydrobenzoic acid, obtained as a by-product in the preparation of the lactam (IV), was isolated as the ethyl ester without the liner (the final solution was alkaline); but it was obtained as the free acid when the liner was used Due to the large ratios of catalyst to reactants the reductions of the nitro group were extremely rapid. Without the liner, and regardless of the size of the run, there was only a twenty to thirty degree temperature rise (at 60–70°) and no more than a few hundred pounds pressure increase, if at all. However, with the liner in use these effects were very erratic, perhaps due to the insulating effect of the space between the liner and bomb. The temperature rose rapidly as much as 50–130° and on one occasion with 0.5 mole of the nitro-ester there was a sudden momentary pressure increase of 2000 lbs. Had this been a larger quantity of material a considerable strain might have been placed on the equipment. Without the liners, and using quantities of the ester (IV) up to 0.7 mole, the products and yields agreed very well with those obtained on the 0.05 mole scale.

ethanol was heated and shaken under 150–200 atm. of hydrogen. The reduction of the nitro group was exothermic between 60° and 100° and over a period of fifty minutes between 120° and 130° the fourth mole of hydrogen was absorbed. The filtered solution was distilled to a small volume, dissolved in benzene, washed with water and 5% sodium bicarbonate, and dried over magnesium sulfate. Distillation of the product gave a slight forerun of 1.5 g. which was followed by 78 g. (87%) of ethyl *m*-aminophenylacetate; b.p. 138–140° (3–4 mm.); n_D^{22} 1.5435.

Anal. Calc'd for $C_{10}H_{13}NO_2$: C, 67.00; H, 7.31; N, 7.82.

Found: C, 66.84; H, 7.37; N, 7.99.

The *hydrochloride* was obtained as fine leaflets from ethanol–ether; m.p. 129–131°.

Anal. Calc'd for $C_{10}H_{14}ClNO_2$: C, 55.67; H, 6.54; Cl, 16.44; N, 6.49.

Found: C, 55.82; H, 6.59; Cl, 16.13; N, 6.83.

m-Aminophenylacetic acid. A mixture of 17.9 g. (0.1 mole) of the ethyl ester of *m*-aminophenylacetic acid and 20 ml. of 6.0 *N* sodium hydroxide was refluxed for thirty minutes. The alcohol was boiled off and 20 ml. of 6.0 *N* hydrochloric acid was added; yield, 14.5 g., m.p. 146–148° [literature (21); 148–149°].

Ethyl 3-aminocyclohexaneacetate (V). To a solution of 4 g. of dry hydrogen chloride in 150 ml. of absolute ethanol was added 17.9 g. (0.1 mole) of ethyl *m*-aminophenylacetate and 1.3 g. of Adams platinum oxide catalyst (American Platinum Works). After two hours of shaking at 60–65° and 30–40 lbs. hydrogen pressure the hydrogen uptake had ceased at the calculated amount. The catalyst was filtered, the alcohol was distilled to a small volume, and the residue was taken up in ether and water. Evaporation of the ether left 0.7 g. of ethyl hexahydrobenzoate. The aqueous solution was basified over chloroform with 20 ml. of 6.0 *N* sodium hydroxide. The chloroform extracts were dried and distilled to give 11.8 g. (64%) of the hexahydro ester boiling at 110° (6 mm.) and 4.2 g. of a fraction with a b.p. of 195–200° (6 mm.).

Lactam of cis-3-aminocyclohexaneacetic acid (VI). *A. Via platinum reduction.* The 11.8 g. of the *cis* and *trans* esters was dissolved in 45 ml. of absolute ethanol and heated at 200° for an hour and a half. After distillation 2.1 g. of the lactam (VI) was obtained by crystallization from ether; m.p. 156–164°. Including 0.3 g. recovered after the distillation of the filtrate the yield amounted to 27%. Several recrystallizations of a sample from ether gave clear colorless prisms; m.p. 163.5–165.5°.

Anal. Calc'd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06.

Found: C, 69.28; H, 9.53; N, 10.33.

After the lactam had been removed the residue was fractionated and gave 7.3 g. (62%) of *ethyl trans-3-aminocyclohexaneacetate*; b.p. 110° (6 mm.), n_D^{22} 1.4650. When a sample of this ester was again heated in ethanol for three hours at 210° no lactam was obtained; thus the ratio of *cis* to *trans* must have been about 3:7.

Anal. Calc'd for $C_{10}H_{19}NO_2$: C, 64.80; H, 10.31; N, 7.56.

Found: C, 64.69; H, 10.28; N, 7.79.

A solution (clear at room temperature, cloudy when warmed) of 3.0 g. of the *trans* ester in 10 ml. of water was refluxed for twenty-four hours. The residue after evaporation of the water was triturated with alcohol to give 2.1 g. (82%) of *trans-3-aminocyclohexaneacetic* acid, m.p. 258–260° dec. A sample was sublimed and recrystallized from water–alcohol to give clusters of tiny needles, m.p. 266–267° dec. (sealed tube).

Anal. Calc'd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91.

Found: C, 61.29; H, 9.73; N, 8.92.

When the mixture of *cis* and *trans* esters has hydrolyzed in the same manner and a 1.0-g. sample of the resulting amino acids was heated at 260° for half an hour in a N_2 atmosphere there was obtained 0.25 g. (28%) of the lactam (VI). The *trans* acid polymerized and gave no lactam under the same conditions.

One and three tenths grams of the *trans* ester after treatment with benzoyl chloride followed by a room temperature saponification gave 1.5 g. of the *benzoate of trans-3-aminocyclohexaneacetic acid*, m.p. 151–156°. Three crystallizations from acetone gave tiny clusters

of fine needles which, when heated slowly, started to melt at 156–157° then resolidified and finally melted at 183–185°.

Anal. Calc'd for $C_{15}H_{19}NO_3$; C, 68.93; H, 7.33; N, 5.36.
Found: C, 68.93; H, 7.46; N, 5.41.

cis-3-Aminocyclohexaneacetic acid. A solution of 2.0 g. of the lactam (VI) in 20 ml. of 1.0 *N* sodium hydroxide was heated at 200° for six hours. After the addition of 20 ml. of 1.0 *N* hydrochloric acid the water was evaporated under a current of air on the steam-bath. The residue was sublimed at 220° (6 mm.) and was then extracted with boiling ether (0.5 g. of lactam was recovered) to leave 1.5 g. of the amino acid. Recrystallization from alcohol-water gave fine needles, m.p. 272–273° dec. (sealed tube). A mixture with the *trans* acid melted at 251–255° with decomposition.

Anal. Calc'd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91.
Found: C, 61.04; H, 9.36; N, 9.26.

One-half gram of the *cis* amino acid heated in a N_2 atmosphere for thirty minutes at 260° gave 0.40 g. (90%) of the lactam (VI).

A 0.47-g. sample of the amino acid gave 0.56 g. of the *benzoate* of *cis-3-aminocyclohexaneacetic acid,* m.p. 185–190°. After recrystallization from acetone fine hair-like needles were obtained which started melting at 185–187° leaving a little solid; if the capillary was then removed from the bath momentarily the sample recrystallized and subsequently melted at 191–192°.

Anal. Calc'd for $C_{15}H_{19}NO_3$: C, 68.93; H, 7.33; N, 5.36.
Found: C, 68.82; H, 7.19; N, 5.53.

A mixture with the *trans* benzoate sintered at 147° and melted at 149–155°.

B. From m-aminophenylacetic acid via Raney nickel reduction. To a solution of 15.1 g. (0.1 mole) of *m*-aminophenylacetic acid in 16.7 ml. of 6.0 *N* sodium hydroxide there was added 12 g. of Raney nickel and 45 ml. of *tert*-butyl alcohol (Eastman). Two and a half moles of hydrogen were absorbed after an hour and a half at 200° and 300 atm. The product was washed out with water and after filtration and washing of the catalyst the solution was distilled to a small volume and 16.5 ml. of 6.0 *N* hydrochloric acid was added. A small amount of insoluble material was removed, the water was evaporated, and the residue was sublimed at 210° (3–5 mm.). A total of 10.5 g. of sublimate was collected, extracted with boiling benzene, and triturated with absolute ethanol to leave 5.4 g. of amino acid; m.p. 240–250° (dec.). From the benzene extracts there was recovered 2.2 g. of the lactam (VI), m.p. 155–162° alone and when mixed with the lactam from *A*.

A 1.0-g. sample of the amino acid heated at 260° for thirty minutes gave 0.60 g. of the lactam. Assuming that the lactam obtained from the benzene solution originated during the sublimation, the total yield of amino acid from this reduction was 50% and the ratio of the *cis* to *trans* isomers must have been approximately 5:1.

C. From ethyl m-nitro-O-benzoylmandelate (III) *via Raney nickel reduction.* A suspension of 165 g. (0.5 mole) of ethyl *m*-nitro-O-benzoylmandelate and 85 g. of Raney nickel in 325 ml. of *tert*-butyl alcohol was shaken and heated up to 200° over a one-hour period during which 4–5 mole-equivalents of hydrogen were consumed.[10] A total of 10–11 mole-equivalents of hydrogen were taken up after 3–5 hours at 200°. Distillation of the product gave 45 g. of ethyl hexahydrobenzoate; b.p. 85–90° (50 mm.) and 50–55 g. (the last half solidified) of material boiling over the range 110–170° (3–5 mm.). This distillate was dissolved in water and ether; the ether was extracted with water and the combined aqueous solutions were acidified to *p*H 2 with 2–3 ml. of 6 *N* hydrochloric acid. The acidic solution was washed with ether and the ether was discarded; then 4–5 ml. of 6 *N* sodium hydroxide was added, the solution was extracted with ether and the ether was again discarded. The aqueous solution was distilled to a small volume and adjusted to *p*H 7–8 (Universal paper). The residue was evaporated dry and sublimed at 3–5 mm. and 140–150°. The 25–28 g. of sublimate was crystallized from acetone–ether to give a total of 22–25 g. (32–36%) of the lactam (VI), m.p. 163.5–165.5° alone and when mixed with lactam from *A*.

Lactam of N-ethyl-cis-3-aminocyclohexaneacetic acid (VII). A suspension of 165 g. (0.5

mole) of the ester (IV), 85 g. of Raney nickel, and 133 g. of sodium carbonate in 300 ml. of absolute ethanol was shaken and heated up to 180° over a one-hour period under 300 atm. of hydrogen.[10] Within two and a half hours at 180° 11–12 mole-equivalents of hydrogen had been consumed. The products were washed out of the bomb with water, filtered, concentrated, and hydrochloric acid (417 ml. of 6.0 *N*) was added in portions. After removing the hexahydrobenzoic acid and further concentrating the solution, alcohol was added to remove most of the sodium chloride. Distillation of the water and alcohol left the amino acid which was lactamized by heating under reflux at 215° (50–60 mm.). The product was distilled directly from the reaction flask with a bath temperature of 200–240° (50 mm.); finally the pressure was reduced to 3–5 mm. and everything distilling up to 150° was collected. The combined distillates (30–35 g.) were dissolved in water and ether. The ether solution was washed twice with water and the combined aqueous solutions were refluxed a few minutes with 5% sodium hydroxide, cooled, and extracted several times with chloroform. The chloroform was washed with 5% hydrochloric acid, the acid solution was washed with chloroform, and the combined chloroform solutions were washed again with 5% sodium hydroxide, dried over potassium carbonate, and distilled to give 23–27 g. (27–32%) of the N-ethyl lactam (VII), b.p. 122–123° (5–6 mm.), n_D^{23} 1.5020.

Anal. Calc'd for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.38.

Found: C, 71.27; H, 10.18; N, 8.68.

After several unsuccessful hydrolyses under milder conditions 3.34 g. (0.02 mole) of the N-ethyl lactam was dissolved in 30 ml. of 2.0 *N* sodium hydroxide and heated in a steel autoclave at 250° for fifteen hours. To the cooled solution was added 10 ml. of 6.0 *N* hydrochloric acid and the unreacted lactam was then recovered by chloroform extraction. Distillation gave 0.91 g. (27%) of unreacted material; n_D^{23} 1.5020. The aqueous solution was evaporated dry at room temperature in a stream of air and the residue was sublimed at 220° (6 mm.) to give 2.4 g. (65%) of *N-ethyl-cis-3-aminocyclohexaneacetic acid*. A sample of the amino acid crystallized from acetone-alcohol-water in fine needles; m.p. 239–240° dec. (sealed tube).

Anal. Calc'd for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34; N, 7.56.

Found: C, 64.78; H, 10.37; N, 7.77.

An 0.85-g. sample of the acid heated at 240° for thirty minutes gave 0.67 g. (87%) of the lactam, n_D^{23} 1.5025.

2-Azabicyclo[3.3.1]nonane (VIII). *A. By copper chromite reduction.* The lactam of *cis*-3-aminocyclohexylacetic acid (VI) (2.8 g.) was hydrogenated at 200–210° and 300 atm. for five hours in 45 ml. of *tert*-butyl alcohol with 9 g. of copper chromite (22). After allowing for the amount of hydrogen taken up by the copper chromite (as determined in a blank run) the absorption of hydrogen was 70–80% of theory. The product was washed out of the bomb with ethanol, filtered, and titrated to *p*H 6. After evaporation of the solvent on the steam-bath the residue was sublimed at 160° (3 mm.) and gave 0.3 g. of unreacted amide. The material which sublimed at 220° was crystallized from alcohol-acetone to give 1.5 g. (46%) of the *hydrochloride* of *2-azabicyclo[3.3.1]nonane*; m.p. 280–295°. A sample was sublimed and recrystallized as sugary prisms or fine needles; m.p. 300–302° dec. (sealed tube).

Anal. Calc'd for $C_8H_{16}ClN$: C, 59.42; H, 9.98; Cl, 21.93; N, 8.66.

Found: C, 59.62; H, 9.90; Cl, 21.80; N, 8.60.

The *free base* (VIII) obtained by basification of an aqueous solution of the hydrochloride and ether extraction, was purified by sublimation at 75–80° (50 mm.) to give a camphoraceous solid, m.p. 135–137° (with partial melting and resolidification at 120–130°).

The *phenylthiourea* derivative crystallized as fine needles from ethanol, m.p. 125–127°.

Anal. Calc'd for $C_{15}H_{20}N_2S$: C, 69.19; H, 7.74; N, 10.76; S, 12.31.

Found: C, 69.05; H, 7.76; N, 10.58; S, 12.13.

B. From the thiolactam (X). A suspension of 7.0 g. (0.05 mole) of the lactam (VI) with 13.3 g. of phosphorus pentasulfide in 50 ml. of xylene was stirred vigorously and heated at 125–130° for an hour in an oil-bath. The cooled solution was stirred with 100 ml. of 25% sodium hydroxide for half an hour at room temperature and the insoluble thiolactam was filtered, washed with water, and air dried. After sublimation at 200° (6 mm.) and crystalliza-

tion from ethanol there was obtained 6.0 g. (77%) of the thiolactam (X), m.p. 187–196°. Recrystallization of a sample from ethanol gave prisms and leaflets; m.p. 196–198° (sealed tube).

Anal. Calc'd for $C_8H_{13}NS$: C, 61.90; H, 8.44; N, 9.03; S, 20.62.
Found: C, 62.17; H, 8.47; N, 9.21; S, 20.82.

Three grams of the thiolactam (X) in 50 ml. of *tert*-butyl alcohol was heated and shaken with 18 g. of Raney nickel for four hours at 80–85° under 40 lbs. of hydrogen. After removal of the nickel, titration (to *p*H 6) of the filtered solution with 1.0 *N* hydrochloric acid indicated a 70–80% conversion of the thiolactam into basic material. The acidic solution was evaporated dry and sublimed. Crystallization of the sublimate from alcohol-acetone gave 2.0 g. (64%) of fine needles, m.p. 292–298° alone and when mixed with a sample from *A*.

2-Ethyl-2-azabicyclo[3.3.1]nonane (IX). *A. By copper chromite reduction.* A solution of 3.34 g. of the N-ethyl lactam (VII) in 45 ml. of *tert*-butyl alcohol was heated and shaken with 10 g. of copper chromite at 250° under 300 atm. of hydrogen until the theoretical amount of hydrogen had been taken up (two hours). Titration of the filtrate after removal of the catalyst indicated the presence of about 85% of the nitrogen as a free base. The solution was evaporated dry and sublimation gave 3.1 g. (82%) of the *hydrochloride* of *2-ethyl-2-azabicyclo-[3.3.1]nonane*. Crystallization from benzene gave small clusters of tiny needles, m.p. 142–144°. The compound was extremely hygroscopic and could not be exposed to the air for more than a few seconds without liquefaction. For analysis a sample was sublimed in the presence of P_2O_5.

Anal. Calc'd for $C_{10}H_{20}ClN$: C, 63.30; H, 10.63; Cl, 18.69; N, 7.38.
Found: C, 62.92; H, 10.39; Cl, 18.58; N, 7.98.

A sample of the *free base* (IX) was obtained as an oil by basification of the hydrochloride, n_D^{25} 1.488.

B. From VIII. (a) A mixture of 1.25 g. of 2-azabicyclo [3.3.1] nonane and 1.56 g. of ethyl iodide in 5 ml. of benzene was allowed to stand several hours and was then basified. The hydrochloride was sublimed (1.40 g.) and after crystallization from benzene there was obtained 1.1 g., m.p. 139–144° alone and when mixed with a sample prepared as in part *A*.

(b) One half gram of the free base (VIII) was added to 4 g. of Raney nickel in 50 ml. of absolute ethanol and the mixture was shaken for four hours under 30 lbs. of hydrogen at 80°. Sublimation and crystallization of the hydrochloride from benzene gave 0.43 g. (60%), m.p. 142–144° alone and when mixed with a sample from *A*.

C. From the thiolactam (X). A solution of 4.0 g. of the thiolactam in 100 ml. of absolute ethanol, protected with a soda-lime tube, was refluxed for three hours with 25 g. of Raney nickel. Titration of the filtered solution indicated 87% conversion of the thiolactam to free amine. The solvent was removed and the residue was sublimed to give 4.2 g. of the hygroscopic hydrochloride of the amine (IX). Crystallization from benzene gave 3.7 g. (76%) of tiny needles, m.p. 142–144° alone and when mixed with a sample from part *A*.

SUMMARY

1. A procedure has been developed for the preparation of the ethyl ester of *m*-aminophenylacetic acid in a three-step process from *m*-nitrobenzaldehyde.

2. Catalytic hydrogenation of ethyl *m*-aminophenylacetic acid over platinum in alcoholic hydrogen chloride to the corresponding hexahydro derivative gave a *cis-trans* ratio of 3:7. Over Raney nickel in *tert*-butyl alcohol–water at 200° the sodium salt gave a *cis-trans* ratio of 5:1. In ethanol with Raney nickel the ethyl ester gave N-ethyl-3-aminocyclohexaneacetic acid.

3. Raney nickel in *tert*-butyl alcohol under hydrogen has been used for the reduction of a thiolactam to the corresponding cyclic amine. In refluxing ethanol the N-ethyl amine was obtained.

4. The synthesis of 2-azabicyclo[3·3·1]nonane and several of its derivatives has been described.

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[Contribution from the Laboratory of Organic Chemistry, Radium Institute, University of Paris]

THE REACTION OF α-HALOGENATED ARYLALKANES WITH METAL POWDERS IN HYDROXYLATED MEDIA[1]

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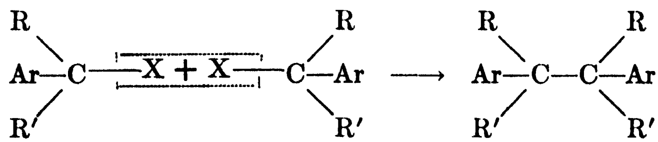
One problem most frequently encountered in preparative organic chemistry is the removal of the halogen atom from α-halogenated arylalkanes with coupling of the remaining radical, resulting in the formation of symmetrical diarylalkanes (I) according to the following scheme:



I II

Two important methods have hitherto been devised to meet this problem: 1. The use of alkali or earth-alkali metals in anhydrous media (especially ethyl ether) as was originated by Wurtz and Fittig, some modifications being introduced later by different authors (1) who recommended the use of various metals (Al, Mg, Zn) or alloys (such as the liquid alloy of potassium and sodium); 2. The excellent method of Kharasch and his co-workers (2) based upon the reduction of Grignard compounds by cobaltous chloride with subsequent dimerization of the free radicals thus liberated.

Although these methods have proven to be of the greatest value for various syntheses, they both require the use of anhydrous solvents, with all the inconveniences inherent in that technique. The second method necessitates also the intervention of very low temperatures, while yields obtained by the former are generally low in the case of arylalkanes bearing halogens adjacent to a secondary or tertiary carbon; these lose a molecule of halogen acid easily in the presence of strong electropositive metals under anhydrous conditions.

A few years ago, Ogata, Turuta, and Oda (3) found that benzyl and benzal chlorides could be reacted in aqueous medium with iron powder to give dibenzyl and stilbene. Although it has no special significance for the preparation of the substances cited, this observation prompted us to investigate the possibility of using iron, as well as other more or less active metal and alloy powders in aqueous or other hydroxylated media for the synthesis of symmetrical diarylalkanes and diarylethylenes not readily prepared through routine methods. Since our work began, Sisido and Nozaki (4) have reported the preparation with low yields (ranging from 5 to 15%) of 2,3-diphenylbutane, 3,4-dianisylhexane, and two

[1] This paper is part of a more general investigation into estrogenic substances. For earlier reports, see (25).

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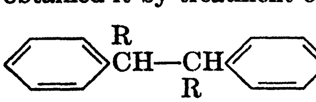
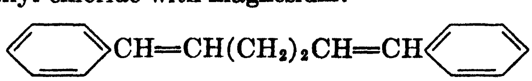
analogous compounds by treatment of the appropriate α-chloro- or α-bromoarylalkanes with iron powder in hot water.

The present work records the results we have obtained in numerous syntheses of symmetrical diarylalkanes (II), using a great variety of chloro- and bromo-compounds of type (I), and many metal or alloy powders, some of which were even superior to the initial iron powder. In some standard cases, the influence of temperature, solvents, and catalysts has also been ascertained. It was found that upon the choice of the metal and quality of samples used, and of the experimental conditions, depend not only the yields but also the nature of the reaction-products. All the substances, the syntheses of which are reported here, and many of which were hitherto unknown, have to a greater or lesser degree some biological interest, either on account of their own physiological activity, or of their connection with natural products.

Synthesis of hydrocarbons. meso-3,4-Diphenylhexane (III), a key substance in the chemistry of synthetic hormonal compounds, and weakly estrogenic itself (5), was readily obtained along with its racemic isomer, by the coupling of α-chloropropylbenzene ($C_6H_5CHClCH_2CH_3$), under the influence of hydrogen-reduced iron powder. α-Chloroamylbenzene ($C_6H_5CHCl(CH_2)_3CH_3$), gave under the same conditions a mixture of a liquid 5,6-diphenyldecane (which we assume to be the racemic compound), with a solid isomer, presumably *meso*-5,6-diphenyldecane (IV). Coupling of cinnamyl chloride was also achieved, giving a complex mixture of many hydrocarbons, from which small quantities of dicinnamyl (V) could be isolated in a pure state. It may be observed that the foregoing substance has recently been identified as the *trans,trans*-derivative by Koch (6), who obtained it by treatment of cinnamyl chloride with magnesium.

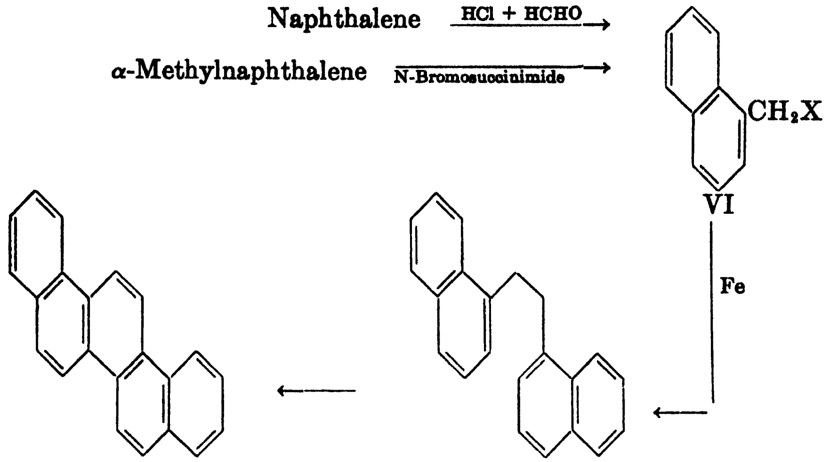


III. R = C_2H_5 IV. R = n-C_4H_9



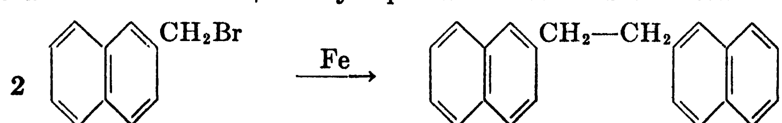
V

In the naphthalene series, 1,2-di-(α,α'-naphthyl)ethane (VII) was easily made either from α-chloromethylnaphthalene (VI, X = Cl) [readily obtainable from naphthalene and formaldehyde in 60% yield, following routine methods (7)], or even better from α-bromomethylnaphthalene (VI, X = Br) [readily prepared by side-chain bromination of α-methylnaphthalene according to Buu-Hoï and Lecocq (8)]. As 1,2-di-(α,α'-naphthyl)ethane is easily convertible into picene under the dehydrogenating influence of aluminum chloride, following the Ruzicka-Hösli reaction (9), these observations offer a convenient three-step synthesis of picene (VIII) from naphthalene or α-methylnaphthalene in at least 10% over-all yield. As it is known that dimethylnaphthalenes are very readily converted into side-chain monobromo compounds (8, 10), our synthesis provides a means of preparing various dimethylpicenes, some of them being of biological significance through their connection with the triterpenes and with the carcinogenesis problem. This modification of the Ruzicka picene synthesis represents an important simplification over the original procedure which started from α-tetralone and β-1-naphthylethanol (11).



VIII VII

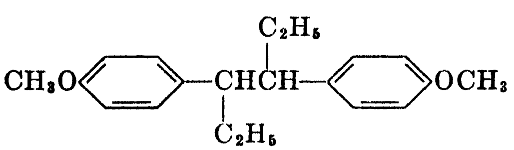
Also in the naphthalene series, we obtained with satisfactory yield 1,2-di-(β,β'-naphthyl)ethane (X) from β-bromomethylnaphthalene (IX), prepared by side-chain bromination of β-methylnaphthalene with N-bromosuccinimide (12).



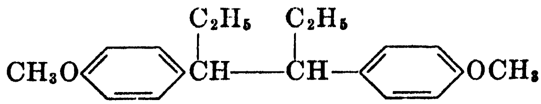
IX X

1,2-di-(β,β'-naphthyl)ethane could be expected to yield 3,4,5,6-dibenzophenanthrene, a slightly carcinogenic, rare hydrocarbon (13), upon treatment with aluminum chloride, but no conclusive results have yet been obtained in that respect.

Synthesis of dl- and meso-3,4-dianisylhexane. Sisido and Nozaki (4) reported a 10% yield of *meso*-3,4-dianisylhexane (XI) on treatment of anethole hydrochloride with iron powder in a mixture of ligroin and hot water, and a 15% yield of the same product when anethole hydrobromide was used. No mention of racemic 3,4-dianisylhexane was made on this occasion. We have found that by



XI



XII

using very fine, hydrogen-reduced iron and introducing slight modifications

into the technique of the Japanese workers, we nearly doubled the yield of *meso*-3,4-dianisylhexane from anethole hydrochloride, and that amounts of the *dl*-isomer (generally obtained in an oily state, which is due to the presence of the dissolved *meso*-form) roughly equivalent to those of the *meso*-compound were always encountered when iron was the reagent, so that a 40% conversion of anethole into 3,4-dianisylhexanes could thus be achieved in aqueous medium. This latter point is of practical importance considering the possibility of stereomutation of XII into XI under the influence of certain catalysts, such as hydrogen sulfide or iodine (14) or ultraviolet irradiation.

Replacement of reduced iron by Raney alloy enhanced the yield of each isomer to about 21%, and if Raney nickel was used, 25% of the *meso*-compound was reached, at the expense of the *dl*-form. Addition to iron powder of iodine as a catalyst produced a slightly favorable effect, while other substances such as cobalt or nickel chloride had apparently no such effect.

A remarkable feature of this coupling reaction is that the *dl-meso* ratio could be augmented by the replacement of the foregoing active metals or alloys by relatively "weak" ones. For instance, the yields of *meso* registered with Devarda's alloy, zinc, and magnesium powder were considerably lower than those of the racemic form, and even in the case of hydrogen-reduced copper powder, no traces of the crystalline *meso* could be isolated, whereas the *dl*-compound was obtained in high yield and in spontaneous crystalline condition. The favorable effect of copper upon the formation of *dl*-3,4-dianisylhexane was also perceptible when the zinc-copper couple was used, the amount of *meso* obtained being smaller than in the case of pure zinc powder. It may be mentioned that addition to water of other hydroxylated solvents, such as alcohols, did not give any interesting results.

Methylmagnesium iodide has been recommended by Sisido and Nozaki (4) for the demethylation of *meso*-3,4-dianisylhexane, but we have found for that purpose a most convenient device in the use of pyridine hydrochloride.

Recent investigations suggest that the activity of stilbestrol and other estrogenic substances for the control of prostatic cancer does not run strictly parallel to their estrogenic potency as measured by the Allen-Doisy test (15). This led us to a quest for substances with structures closely related to stilbestrol or hexestrol, but with little or no estrogenic properties. The preparation of a series of new ethers of hexestrol listed in Table I was part of that scheme of research. They are now under clinical investigation by Professor Lacassagne and Dr. Corre, especially in cancer of the lung. Unlike the stilbestrol series, in which many ethers are known, only a few ethers of hexestrol have hitherto been prepared and tested for estrogenic potency (16).

Synthesis of isomers and homologs of the 3,4-dianisylhexanes. Coupling of α-chloroarylalkanes by metal powders in aqueous medium was found to be a convenient way to obtain a series of isomers and homologs of *dl*- and *meso*-dianisylhexane, which were intermediates in the synthesis of isomers and homologs of hexestrol. These latter were required for biological investigation in the line of medical research indicated in the preceding section.

o-(α-Hydroxypropyl)anisole (XIII), obtained from *o*-methoxybenzaldehyed and ethylmagnesium bromide, was converted by dry hydrogen chloride into *o*-(α-chloropropyl)anisole (XIV), and this underwent the usual coupling reaction with iron powder or Raney nickel to give a mixture of a *liquid* and a *solid* 3,4-di-(*o*-methoxyphenyl)hexane (XV). By analogy with the *para*-isomers, we assign

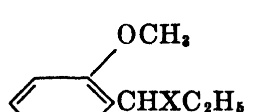
TABLE I

NEW DIETHERS OF HEXESTROL

p—$ROC_6H_4CH(C_2H_5)CH(C_2H_5)C_6H_4OR$—$p$

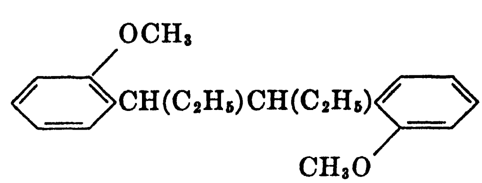
R	FORMULA	M.P., °C.	ANALYSES			
			Calc'd		Found	
			C	H	C	H
Ethyl	$C_{22}H_{30}O_2$	133	80.9	9.2	81.1	9.3
n-Propyl	$C_{24}H_{34}O_2$	110	81.3	9.6	81.2	9.6
Isopropyl	$C_{24}H_{34}O_2$	115	81.3	9.6	81.2	9.8
Isobutyl	$C_{26}H_{38}O_2$	109	81.6	9.9	81.6	10.1
Isoamyl	$C_{28}H_{42}O_2$	83	81.9	10.2	81.8	10.1
n-Hexyl	$C_{30}H_{46}O_2$	73	82.2	10.5	82.1	10.6
n-Octyl	$C_{34}H_{54}O_2$	66	82.5	10.9	82.4	10.8
n-Decyl	$C_{38}H_{62}O_2$	57	82.8	11.4	82.4	11.2
n-Dodecyl	$C_{42}H_{70}O_2$	79	83.1	11.6	83.3	11.6
n-Tetradecyl	$C_{46}H_{78}O_2$	65	83.3	11.7	83.2	11.7
n-Hexadecyl	$C_{50}H_{86}O_2$	72	83.5	12.0	83.3	12.2
n-Octadecyl	$C_{54}H_{94}O_2$	92	83.6	12.2	83.6	12.3
Benzyl	$C_{32}H_{34}O_2$	219	85.3	7.5	85.2	7.6
p-Chlorobenzyl	$C_{32}H_{32}Cl_2O_2$	194	73.9	6.1	73.6	6.2
2,5-Dimethylbenzyl	$C_{36}H_{42}O_2$	198	85.4	8.3	85.8	8.6
β-Phenylethyl	$C_{34}H_{38}O_2$	119	85.3	8.0	85.6	8.0
γ-Phenylpropyl	$C_{36}H_{42}O_2$	157	85.4	8.3	85.6	7.2
α-Naphthylmethyl	$C_{40}H_{38}O_2$	233	87.2	6.9	87.0	7.0
Cinnamyl	$C_{36}H_{38}O_2$	180	86.0	7.8	86.2	7.9

the racemic structure to the liquid, and the *meso*-structure to the solid. De-



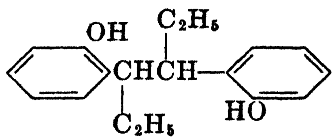
XIII X = OH

XIV X = Cl

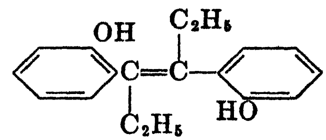


XV

methylation of the latter with pyridine hydrochloride readily yielded *meso*-3,4-di-(*o*-hydroxyphenyl)hexane (XVI), ("Orthohexestrol"). It may be recalled in that respect that the analog of this compound in the stilbestrol series, 2,2′-dihydroxy-α,β-diethylstilbene (XVIII), already prepared by Dodds, *et al.* (17), is considerably less estrogenic than the *para*-isomer.

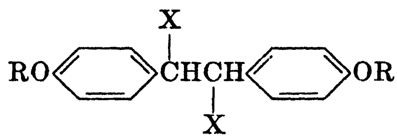


XVI



XVII

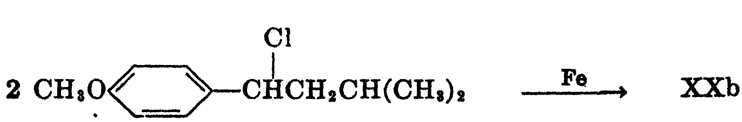
A drop in potency has also been recorded by the preceding authors when the two ethyl groups in hexestrol are replaced by *n*-propyl groups, resulting in *meso*-4,5-di-(*p*-hydroxyphenyl)octane (XVIIIa). This substance was prepared with great difficulty by hydriodic acid demethylation of the solid dimethyl ether (XVIIIb) obtained in the catalytic hydrogenation of 4,4′-dimethoxy-α,β-di-*n*-propylstilbene, along with a liquid isomer. We prepared (XVIIIb) much more conveniently from *p*-(α-hydroxybutyl)anisole following the normal sequence of reactions, and its demethylation with pyridine hydrochloride gave (XVIIIa)



XVIIIa	R = H, X = *n*—C_3H_7;	XVIIIb	R = CH_3, X = *n*—C_3H_7
XIXa	R = H, X = *n*—C_4H_9;	XIXb	R = CH_3, X = *n*—C_4H_9
XXa	R = H, X = *iso*—C_4H_9;	XXb	R = CH_3, X = *iso*—C_4H_9
XXXIa	R = H, X = *iso*—C_5H_{11};	XXIb	R = CH_3, X = *iso*—C_5H_{11}

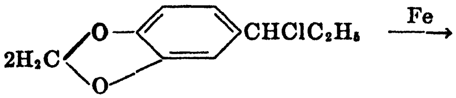
in very high yield. A liquid isomer, apparently identical with that of Dodds, *et al.* was also encountered during the preparation of (XVIIIb), and its demethylation gave the *liquid* 4,5-di-(*p*-hydroxyphenyl)octane mentioned by the above authors.

Following a similar procedure, and starting from *p*-(α-chloroamyl)anisole by saturating with hydrogen chloride either 4-methoxy-β-*n*-propylstyrene or *p*-(α-hydroxyamyl)anisole (both obtained from anisaldehyde and *n*-butylmagnesium bromide), we prepared a *solid* 5,6-di-(*p*-hydroxyphenyl)decane, believed to be the *meso*-form (XIXa), *via* a *solid* 5,6-dianisyldecane (XIXb). The latter was accompanied by a high proportion of a *liquid* isomer, which was demethylated to a *liquid* 5,6-di-(*p*-methoxyphenyl)decane. It is remarkable that coupling of *p*-(α-chloroisoamyl)anisole [prepared from anisaldehyde and isobutylmagnesium bromide and subsequent hydrogen chloride treatment either of the carbinol itself or of its dehydration product, 4-methoxy-β-isopropylstyrene *p*-$CH_3OC_6H_4$—CH=CHCH$(CH_3)_2$] yielded an unusually high proportion of a *solid* 2,7-dimethyl-4,5-dianisyloctane, probably (XXb), with only minute quantities of the *liquid* isomer expected. This is probably a steric effect due to the branching of the two molecules of *p*-(α-chloroisoamyl)anisole to be coupled, the *meso*-configuration being thus favored at the expense of the sterically hindered racemic form.

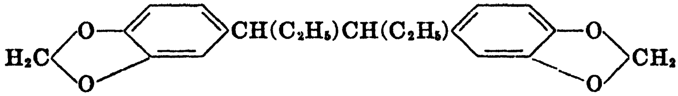


Also consistent with this view is our failure to obtain any significant amount of coupling product from p-(α-chloroisobutyl)anisole p-$CH_3OC_6H_4CHClCH(CH_3)_2$. On the contrary, p-(α-chloroisohexyl)anisole [prepared by addition of hydrogen chloride to 4-methoxy-β-isoamylstyrene p-$CH_3OC_6H_4CH=CH(CH_2)_2CH(CH_3)_2$] gave good yields of a coupling product, which could not be resolved into a *meso*-(XXIb) and a *dl*-isomer, although demethylation produced a solid diphenol, probably *meso*-2,9-dimethyl-5,6-di-(p-hydroxyphenyl)decane (XXIa). p-(α-Chlorohexyl)anisole p-$CH_3C_6H_4CHCl(CH_2)_4CH_3$ also gave high yields of a liquid coupling product, probably a mixture of *dl*- and *meso*-6,7-dianisyldodecane.

Coupling of chloro derivatives of polyphenol ethers. The coupling reaction of α-chloroarylkanes by metal powders in aqueous medium can be extended to the syntheses of complicated molecules such as those bearing fragile ether groups.



XXII

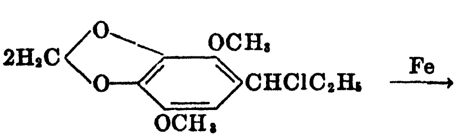


XXIII

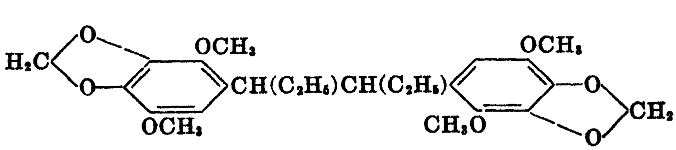
The adduct (XXII) of one molecule of hydrochloric acid to isosafrole was thus readily converted into a mixture of a liquid and a solid 2,3-di-(m,p-methylenedioxyphenyl)hexane (XXIII). For reasons of analogy, we assign the *meso*-structure to the solid isomer, which could thereby be related to the 3,4-(m,p-dihydroxyphenyl)hexane m.p. 231–232°, already prepared by Short (18).

The adduct (XXIV) of hydrochloric acid and isoapiole similarly underwent a coupling reaction, giving a mixture of 2,3-di-(2,5-dimethoxy-3,4-methylenedioxyphenyl)hexanes (XXV), from which a small amount of a *solid* substance believed to be the *meso*-form could be isolated.

The results of the biological investigations undertaken by Professor A. Lacassagne and Dr. I. Corre upon the substances described in this paper will be published elsewhere.



XXIV



XXV

EXPERIMENTAL

Coupling of α-chloropropylbenzene. This substance (120 g.) was obtained in 98% yield by saturating ethylphenylcarbinol with dry hydrogen chloride at room temperature; the organic layer was decanted from the water formed, and washed thoroughly three times with iced-water. It was then added in small portions to a well-stirred mixture of pure hydrogen-reduced iron powder (60 g.) (purchased from Rhône-Poulenc, and obtained from the pure oxide by reduction with hydrogen at low temperature), and water heated to about 90–95° (250 ml.). A lively reaction set in accompanied by coloration of the water to pale green; following the addition, the mixture was boiled for thirty minutes. After cooling, the iron powder in excess was filtered off, washed with benzene, and the two-layer filtrate thoroughly extracted with the same solvent. The solvent was removed, and the residue vacuum-distilled. The forerun (50 g.) consisted mainly of propenylbenzene (bromine-test) and unchanged α-chloropropylbenzene, and was followed by 22 g. of the coupling product, b.p. 170–176°/13 mm. This partly solidified in the refrigerator, giving 6 g. of *meso*-3,4-diphenylhexane, crystallizing from methanol in colorless, shiny rods, m.p. 88–89° [the melting points recorded in the literature vary from 83–84° (19) to 93° (20)]. After some time in the refrigerator, the filtrate again deposited 1.5 g. of that compound; the remaining liquid was then rectified, giving 12 g. of a colorless oil, b.p. 170–172°/13 mm., considered to be the *dl*-isomer. The yields of 3,4-diphenylhexanes were slightly higher when α-bromopropylbenzene (prepared by bubbling dry hydrobromic acid into ice-cooled ethylphenylcarbinol) was used for coupling.

Coupling of α-chloroamylbenzene. Butylphenylcarbinol (120 g.) was saturated with dry hydrogen chloride, and the α-chloroamylbenzene thus obtained was treated with iron powder (55 g.) in hot water as above. The reaction was much less perceptible than for the lower homolog. Yield, 6 g. of coupling product, b.p. 200–205°/15 mm., which yielded 2 g. of a solid after prolonged standing at −10° in methanol. After recrystallization from acetone, long colorless, shiny needles, m.p. 77°, probably *meso*-diphenyldecane, were obtained.

Anal. Calc'd for $C_{22}H_{30}$: C, 89.8; H, 10.2.

Found: C, 89.7; H, 10.4.

The liquid isomer (3.5 g.) was a colorless, rather fluid oil, b.p. 200–203°/15 mm.

Anal. Calc'd for $C_{22}H_{30}$: C, 89.8; H, 10.2.

Found: C, 89.8; H, 10.5.

Redistillation of the forerun obtained in this experiment gave 100 g. of pure α-chloroamylbenzene in the form of a mobile, colorless liquid, b.p. 130–135°/15 mm.; decomposing on boiling at ordinary pressure.

Anal. Calc'd for $C_{11}H_{15}Cl$: C, 72.3; H, 8.2.

Found: C, 72.1; H, 8.1.

Coupling of cinnamyl chloride. When 125 g. of the chloride, b.p. 225–228°/17 mm., was treated in the usual way with 60 g. of iron powder in hot water (200 ml.) there was little apparent reaction. After working up the mixture in the usual manner, 35 g. of a higher-boiling fraction was obtained in the form of a very viscous, brown-yellow oil, b.p. 205–220°/10 mm., which crystallized partially; the solid was recrystallized from alcohol, giving *trans-trans*-dicinnamyl in the form of glistening, colorless leaflets, m.p. 81–82°. After a prolonged stay in the refrigerator, the mother liquors yielded a further crop of the same compound (yield, 6 g.). No attempts were made to isolate pure isodicinnamyl.

1,2-Di-(α,α'-naphthyl)ethane (VII). (*a*) α-Chloromethylnaphthalene (26 g.) was treated with a great excess of iron powder (20 g.) in boiling water (100 ml.) for two hours. The reaction product was taken up in benzene, and gave, after the usual treatment, 17 g. of unchanged α-chloromethylnaphthalene (b.p. 158–160°/13 mm.) and 5 g. of 1,2-di-(α,α'-naphthyl)ethane, b.p. 275–278°/13 mm., crystallizing from a mixture of alcohol and benzene in colorless prisms, m.p. 161–162° [Bamberger and Lodter (21) described this compound as yellow-green plates, m.p. 160°].

(*b*) α-Bromomethylnaphthalene (10 g.) was prepared from α-methylnaphthalene and N-bromosuccinimide in the presence of some benzoyl peroxide and in carbon tetrachloride solution (yield, over 75%); treated as above with iron powder, it gave 4 g. of 1,2-di-(α,α'-

naphthyl)ethane. Similar results were obtained when Raney nickel was substituted for iron powder.

A solution of 10 g. of the latter compound in 50 ml. of carbon disulfide was boiled for two hours on the water-bath with 20 g. of finely powdered aluminum chloride. The mixture obtained was poured on to ice, and the semi-solid material formed was extracted with chloroform; the organic layer was dried over sodium sulfate, the solvents removed, and the residue crystallized from xylene, giving *picene* in the form of needles, m.p. 365°. The mother liquors from this operation gave on vacuum-distillation some unchanged dinaphthylethane and then a further quantity of picene (total yield, 4 g.).

1,2-Di-(β,β'-naphthyl)ethane (*X*). β-Bromomethylnaphthalene (10 g., prepared from β-methylnaphthalene and N-bromosuccinimide as for the α-isomer), treated as above with 10 g. of iron powder, yielded 5 g. of 1,2-di-(β,β'-naphthyl)ethane, crystallizing from benzene in colorless prisms, m.p. 255° [Bamberger and Lodter (21) gave m.p. 253°]. After treatment with aluminum chloride in carbon disulfide solution for two hours, this compound was partly changed into a mixture of many high-boiling hydrocarbons, the constitution of which is being investigated.

COUPLING OF p-α-CHLOROPROPYLANISOLE

This compound was prepared in almost quantitative yield by saturating ice-cooled ethylanisylcarbinol mixed with some petroleum ether (b.p. 50–90°) with dry hydrochloric acid; the addition of hydrogen chloride to anethole is nevertheless a more convenient method, although the yields of p-α-chloropropylanisole are substantially lower. The yield of the addition could be increased by certain catalysts such as stannous chloride.

(*a*) *By hydrogen-reduced iron powder*. An ice-cooled mixture of 200 g. of crystallized anethole and 40 ml. of petroleum ether was saturated with dry hydrogen chloride and the dark colored liquid obtained was thoroughly washed with iced water, which produced decoloration into pale pink. The liquid was added in small portions (10 ml.) to a well-stirred mixture of 80 g. of hydrogen-reduced iron powder and 1,000 ml. of water previously heated at 75–80°; a lively reaction was noticeable after each addition, most of the petroleum ether being allowed to distil off. After the addition, the reaction mixture was boiled for 30 minutes and then left overnight at 2°. The upper organic layer had by then partly solidified; the *meso*-2,3-dianisylhexane and the iron powder in excess were filtered off and XI separated by extraction with benzene; evaporation of the solvent and crystallization of the residue from methanol gave 17 g. of the *meso*-compound, m.p. 147–148°. The filtrate was extracted with benzene, the solvent removed, and the remaining oil vacuum-distilled. After the forerun (50 g. of anethole, b.p. 232°, containing some propylanisole, b p. 212–218°), 62 g. of an oil was obtained, b.p. 222–235°/13 mm., which partly solidified, giving a further crop of XI; the remaining oil was dissolved in methanol, and the mixture kept some time in the refrigerator, yielding a third crop of XI (total yield, 36 g.). The filtrate from this operation was distilled, and 41 g. of the racemic compound, b.p. 225–230°/13 mm. was thus obtained. Attempts to increase the yields by addition of cobalt or nickel chloride (1 g.) did not succeed, nor did the addition of alcohol or dioxane. Addition of iodine (0.5 g.) or substitution of anethole hydrobromide for α-chloropropylanisole raised the yield to about 45% of a mixture of roughly equal amounts of the two forms.

In the following experiments, the weight of reagents is the same as above. As in the case of iron, the dispersion grade and the quality of the metal or alloy powder has an important influence upon the yields. Unless otherwise stated, the *dl*-form referred to was not quite pure and therefore remained in the liquid state.

(*b*) *By aluminum powder:* the reaction was very energetic, but the mixture of isomers obtained (35 g.) yielded little of the *meso*-form.

(*c*) *By Raney alloy:* yield, 41 g. of the *meso*-form (m.p. 148°) and 42 g. of the *dl*-form; 35 g. of anethole recovered.

(*d*) *By Raney nickel catalyst:* yield, 50 g. of the *meso*-form and 16 g. of the *dl*-form.

(*e*) *By Devarda's alloy:* yield, 19.5 g. of the *meso*-form, and 40 g. of the *dl*-form.

(*f*) *By magnesium powder:* the reaction was extremely violent, and yielded 83 g. of an oil consisting mainly of the *dl*-form.

(*g*) *By zinc powder:* the reaction was hardly noticeable at 80°, and the mixture of reagents was therefore boiled for two hours; yield, 15 g. of the *meso*-form and 20 g. of the *dl*-form.

(*h*) *By zinc-copper couple* (zinc powder + copper sulfate): the reaction was violent, and yielded 31 g. of the *meso*-form and 48 g. of the *dl*-form. Very little anethole (8 g.) was recovered.

(*i*) *By hydrogen-reduced copper powder:* the reaction was a considerably weaker one and yielded an oil which rapidly solidified in the refrigerator. After recrystallizations from methanol or ligroin, the solid *dl*-form (50 g.) was obtained in colorless prisms, m.p. 49–53° [Dodds, *et al.* (17) gave m.p. 56–57° for a sample prepared by methylation of *dl*-3,4-dianisylhexane (m.p. 128°)]; 105 g. of anethole was recovered.

Demethylation of meso-3,4-dianisylhexane. A mixture of 300 g. of anhydrous pyridine hydrochloride and 100 g. of *meso*-3,4-dianisylhexane was gently refluxed until the supernatant layer had disappeared. Heating was continued for ten minutes, and the hot reaction product was poured into 1 l. of well-stirred iced-water. The almost colorless solid thus obtained was filtered, thoroughly dried, and crystallized from benzene, giving *meso*-3,4-di-(*p*-hydroxyphenyl)hexane, m.p. 187° [the literature (17) gives m.p. 184–185°], in 92% yield.

Preparation of diethers of hexestrol. The diethyl ether was prepared by adding the calculated amount of diethyl sulfate (2 mol.) to a solution of hexestrol in a slight excess of 20% aqueous NaOH. The precipitate obtained was recrystallized from ethanol. The other diethers were prepared by refluxing for two to four hours a mixture of the alkyl or arylalkyl bromide involved and hexestrol, dissolved in a slight excess of 20% alcoholic potassium hydroxide. The reaction product was poured into an excess of slightly alkaline water, and the precipitate recrystallized from ethanol for the dialkyl ethers, and from toluene for the diarylalkyl ethers, which are generally scarcely soluble in ethanol. In all cases, colorless prisms were obtained in at least 90% yield. A solid diether was also obtained from N-diethylaminoethyl chloride by the same procedure.

Synthesis of "orthohexestrol". Ethyl-*o*-anisylcarbinol was prepared in 82% yield from *o*-methoxybenzaldehyde and ethylmagnesium bromide in the usual way. The carbinol (100 g.) was mixed with 100 ml. of petroleum ether and saturated at −5° with dry hydrogen chloride. The coupling of 1-α-chloropropyl-2-methoxybenzene was effected with iron powder (50 g.) according to the usual procedure. Yield, 17 g. of an oil, b.p. 196–202°/13 mm., which partly solidified in the refrigerator, yielding 3.5 g. of a substance believed to be *meso*-3,4-di-(*o*-methoxyphenyl)hexane. This crystallized from methanol in fine, colorless needles m.p. 102°; the filtrates yielded after some standing at 0° a further crop of the same compound (0.5 g.).

Anal. Calc'd for $C_{20}H_{26}O_2$: C, 80.5; H, 8.7.
Found: C, 80.3; H, 8.8.

The remaining oil was rectified, giving 12 g. of a pale yellow viscous liquid, b.p. 195–202°/13 mm., believed to be *dl*-3,4-di-(*o*-methoxyphenyl)hexane.

Anal. Calc'd for $C_{20}H_{26}O_2$: C, 80.5; H, 8.7.
Found: C, 80.4; H, 8.9.

Demethylation of meso-3,4-di-(o-methoxyphenyl)hexane. The solid isomer (3 g.) and 10 g. of pyridine hydrochloride were refluxed for two hours, and the reaction product worked up as for hexestrol. After recrystallization from benzene, tufts of colorless shiny needles, m.p. 155°, extremely soluble in alcohol, more soluble in benzene than hexestrol, and readily sublimable around the m.p., were obtained. Yield, 96%.

Anal. Calc'd for $C_{18}H_{22}O_2$: C, 80.0; H, 8.2.
Found: C, 79.9; H, 8.4.

This compound should be structurally related to the 2,2′-dihydroxy-α,β-diethylstilbene, m.p. 152–153° prepared by Dodds, *et al.* (17).

SYNTHESES OF HIGHER HOMOLOGS OF HEXESTROL

4,5-Di-(p-hydroxyphenyl)octanes. *p*-(α-Hydroxybutyl)anisole, a pale yellow oil, b.p. 145–146°/13 mm., was obtained in 80% yield from benzaldehyde and *n*-propylmagnesium

bromide in ether. It was transformed by dry hydrogen chloride at −5° into *p*-butenylanisole prepared according to Klages (22). The coupling reaction was performed with iron powder, and the product worked up in the usual way, giving 20 g. of a mixture of 3,5-dianisyloctanes. From the mixture, 8 g. of the solid *meso*-isomer crystallizing from ethanol in shiny colorless prisms m.p. 123°, was obtained [the literature (17) gave m.p. 121–122°, for a specimen prepared by hydrogenation of the corresponding stilbene]. Demethylation of this substance (5 g.) by pyridine hydrochloride (20 g.) gave a 98% yield of *meso*-4,5-di-(*p*-hydroxyphenyl)-octane, crystallizing from toluene in long colorless needles, m.p. 168° (literature m.p. 165°). The residue from the separation of *meso*-4,5-dianisyloctane was rectified, affording *dl*-4,5-dianisyloctane in the form of a pale yellow, viscous oil b.p. 235–236°/13 mm. (yield, 11 g.), which was demethylated by pyridine hydrochloride to the oily *dl*-4,5-di-(*p*-hydroxyphenyl)octane, which did not solidify even after many months (yield, 10 g.).

Coupling of p-(α-chloroamyl)anisole. The reaction of *n*-butylmagnesium bromide upon anisaldehyde in ether gave a mixture of *n-amylanisylcarbinol* (pale yellow liquid b.p. 266–270°) and its dehydration product *4-methoxy-β-n-propylstyrene* (pale yellow, rather mobile liquid, b.p. 254–258°, with a pleasant aromatic odor). The mixture of both substances (70 g.) was saturated at −5° with dry hydrogen chloride, and the resulting *p*-(α-chloroamyl)anisole treated with iron powder as usual. Yield, 33 g. of a coupling product, b.p. 245–246°/13 mm.; this gave, after a long standing in the refrigerator, a small amount of a solid, believed to be pure *meso-5,6-dianisyldecane* (XIXb), which crystallized from ethanol in beautiful shiny tablets, m.p. 84°, easily soluble in hot ethanol.

Anal. Calc'd for $C_{24}H_{34}O_2$: C, 81.3; H, 9.6.

Found: C, 81.0; H, 9.7.

Demethylation of the foregoing compound gave in 98% yield *meso-5,6-di-(p-hydroxyphenyl)decane* (XIXa), crystallizing from benzene in fine, dull colorless needles, m.p. 167–168°.

Anal. Calc'd for $C_{22}H_{30}O_2$: C, 80.9; H, 9.2.

Found: C, 80.7; H, 9.5.

Because of the great solubility of *meso*-5,6-dianisyldecane in its *dl*-isomer, no attempt was made to isolate the latter substance in a satisfactorily pure state.

Coupling of p-(α-chloroisoamyl)anisole. The reaction of isobutylmagnesium bromide upon anisaldehyde in the usual way yielded a mixture of *isoamylanisylcarbinol* and its dehydration product *4-methoxy-β-isopropylstyrene* (b.p. 245–252°) [the latter substance has already been prepared in another way by Puxeddu (23), who gave b.p. 248–252°]. On coupling, *p*-(α-chloroisoamyl)anisole obtained from that mixture (60 g.) yielded 21 g., of a product b.p. 234–235°/13 mm. which readily solidified; after recrystallization from methanol, 18 g. of *meso-2,7-dimethyl-4,5-dianisyloctane* (XXb) was obtained in the form of clusters of colorless plates, m.p. 127–128°, closely resembling silver nitrate.

Anal. Calc'd for $C_{24}H_{34}O_2$: C, 81.3; H, 9.6.

Found: C, 81.2; H, 9.8.

Demethylation of this compound (15 g.) by pyridine hydrochloride (80 g.) resulted, in usual yield, in *meso-2,7-dimethyl-4,5-di-(p-hydroxyphenyl)octane* (XXa), crystallizing from benzene in long, silky colorless needles, m.p. 206–207° (sublimation above 180°).

Anal. Calc'd for $C_{22}H_{30}O_2$: C, 80.9; H, 9.2.

Found: C, 80.6; H, 9.2.

In the mother liquors from the crystallization of (XXb), a small quantity of a resinous material was found. This probably contained the *dl*-isomer.

Coupling of p-(α-chloroisohexyl)anisole. The reaction of isoamylmagnesium bromide with anisaldehyde gave a product which, after repeated distillation, resulted in pure *4-methoxy-β-isobutylstyrene*, a pale yellow, rather mobile oil, b.p. 264–265°, with an aromatic wood odor (yield, 70%).

Anal. Calc'd for $C_{13}H_{18}O$: C, 82.1; H, 9.4.

Found: C, 82.2; H, 9.7.

After addition of hydrogen chloride to the foregoing compound (70 g.) and coupling with

iron powder, there was obtained 30 g. of a *dl-meso*-mixture in the form of a pale yellow, viscous oil b.p. 246°/13 mm., which did not solidify at 0° even after one year.

Anal. Calc'd for $C_{26}H_{38}O_2$: C, 81.6; H, 9.9.

Found: C, 81.4; H, 10.2.

Pyridine-demethylation of that oil resulted in small amounts of a solid compound (along with much resinous material) believed to be *meso-2,9-dimethyl-5,6-di-(p-hydroxyphenyl)-decane* (XXIa), crystallizing from benzene in large colorless prisms, m.p. 119–120°, extremely soluble in methanol.

Anal. Calc'd for $C_{24}H_{34}O_2$: C, 81.3; H, 9.6.

Found: C, 81.0; H, 9.6.

Attempts towards the synthesis of 2,5-dimethyl-3,4-dianisylhexanes. The reaction of isopropylmagnesium bromide upon anisaldehyde gave a mixture (b.p. 230–245°) of isopropylanisylcarbinol and 4-methoxy-β,β-dimethylstyrene. This mixture was dissolved in petroleum ether and saturated at −5° with dry hydrogen chloride, and the resulting product treated with iron powder as usual. A lively reaction was observed, but no coupling could be detected.

COUPLING OF CHLORO DERIVATIVES OF POLYPHENOL ETHERS

Coupling of the hydrogen chloride-adduct of isosafrole. Isosafrole (85 g.) prepared from safrole by treatment with a solution of sodium in isoamyl alcohol (24), was mixed with petroleum ether (50 ml.) and saturated at −5° with dry hydrogen chloride. The resulting α-chlorodihydrosafrole was treated in the usual way with 40 g. of iron powder and 250 ml. of water previously heated at 90°, and the mixture was subsequently boiled for thirty minutes. The reaction was a moderate one, and gave 32 g. of the coupling product in the form of an extremely viscous yellow oil, b.p. 255–268°/13 mm.; this solidified on trituration with ethanol. After several recrystallizations from a mixture of ethanol and benzene, fine colorless prisms, m.p. 175° were obtained. A lower-melting isomer was present in the mother liquors, but could not be completely purified. The higher-melting substance is assumed to be *meso-2,3-di-(m,p-methylenedioxyphenyl)hexane.*

Anal. Calc'd for $C_{20}H_{22}O_4$: C, 73.6; H, 6.7.

Found: C, 73.5; H, 6.8.

Coupling of the hydrogen chloride-adduct of isoapiole. Isoapiole (75 g.), prepared by heating apiole with a solution of potassium hydroxide in ethanol, was dissolved in petroleum ether (150 ml.) and saturated at −5° with dry hydrogen chloride. The coupling reaction was performed as usual, giving 42 g. of a product, b.p. 296–304°/13 mm., in the form of an extremely viscous pale yellow oil. On prolonged standing of its acetone solution this gave a solid (3 g.) which was recrystallized from ethanol, and from acetone. Fine silky, colorless needles m.p. 157° were thus obtained, and this substance is believed to be *meso-2,3-di-(2,5-dimethoxy-3,4-methylenedioxyphenyl)hexane.*

Anal. Calc'd for $C_{24}H_{30}O_8$: C, 64.6; H, 6.7.

Found: C, 64.5; H, 6.8.

In the mother liquors from the crystallization of the supposed *meso*-form, there remained a great quantity of a thick oil which gave after rectification the presumed *dl*-form, b.p. 298–300°/13 mm., which did not solidify even after prolonged standing in the refrigerator.

Anal. Calc'd for $C_{24}H_{30}O_8$: C, 64.6; H, 6.9.

Found: C, 64.3; H, 6.9.

Both isomers charred on prolonged heating with pyridine hydrochloride.

SUMMARY

1. The reaction of different metal and alloy powders upon α-halogenated arylalkanes in hydroxylated media has been examined with a view of developing it into an instrument for various organic syntheses.

2. The preparation by this reaction of a number of substances bearing a biological interest and of intermediates for the syntheses of such compounds is described; in particular, a convenient device is elaborated for the technical preparation of hexestrol.

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[Contribution from the Chemical Laboratory of the University of California]

THE PREPARATION OF CYCLOBUTANECARBOXYLIC ACID

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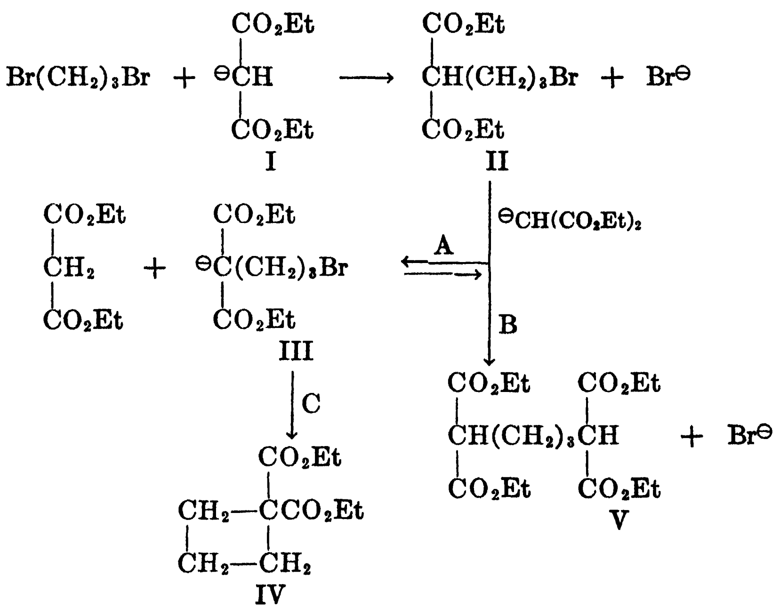
Cyclobutanecarboxylic acid has been the principal starting material for preparation of monosubstituted cyclobutane derivatives, and in a recent paper (1), there was reported a convenient preparation of cyclobutane from this acid. The hydrolysis and decarboxylation of diethyl cyclobutanedicarboxylate has offered no difficulties; however, low yields have always been reported for the preparation of the diester from condensation of trimethylene dibromide with sodio malonic ester. Heisig (2) has reported that his investigations failed to improve the yield of about 25% reported by previous workers, including Perkin (3) who first carried out the reaction in 1887. The preparation in Organic Syntheses (4) gives a similar yield.

Since considerable quantities of cyclobutanecarboxylic acid were required for preparation of cyclobutane, a study was made of the condensation of trimethylene dibromide with sodio malonic ester, and methods have been developed for obtaining the cyclic diester in yields as high as 60%. The reactions involved in this condensation are presented in the accompanying chart.



It will be noted that the critical feature, which determines whether cyclic ester, IV, or tetraester, V, is obtained, is the mode of reaction of malonic ester ion with the bromoester, II, obtained in the first step. Alkylation of the ion, III, with trimethylene dibromide is not considered since the intramolecular reaction, C, is highly favored. Reaction A is a reversible ion exchange, presum-

ably relatively rapid in comparison with the irreversible reactions B and C. If it be assumed that the rates of reactions B and C are of the same order of magnitude, it follows that the relative yields of esters IV and V depend on the position of equilibrium A. Further, if two moles of sodio malonic ester are used for each mole of trimethylene dibromide, so that the full mole of ion, III, may be obtained as indicated in the chart, a mole of malonic ester is liberated for each mole of cyclic diester formed, and the accumulation of this malonic ester shifts equilibrium A to the right so that formation of tetraester, V, is favored during the latter stages of the reaction. Use of an amount of malonic ester in excess of the sodium, as most previous workers have, is especially unfavorable

TABLE I

ALKYLATION OF DIETHYL MALONATE WITH TRIMETHYLENE DIBROMIDE

RUN. NO.	RATIO OF REAGENTS			YIELDS,[a] %	
	Dibromide	Na	M.E.	Diester, IV	Tetraester, V
1	1	2	3	24	52
2	1	3	3	53	16.3
3	1[b]	3	3	49.9	23.9
4	1	2	2	42.8	18.4
5	1	2	1.5	54	12.3
6	1	2[c]	1.1	52.4	8.1
7	1	2[d]	1.2	60.8	7.3

[a] All yields based on trimethylene dibromide. [b] Dibromide added during one hour to the refluxing solution. [c] NaOEt (0.9 equivalent) in ethanol added concurrently with the dibromide, during one hour to the refluxing solution. No malonic ester was recovered in this run, but 2 g. of dibromide was recovered. [d] NaOEt (0.8 equivalent) added concurrently as described in [c]. A small amount of unreacted malonic ester was recovered (5.3 g. of forerun before cyclic ester was collected).

to formation of cyclic ester. It might appear that this difficulty could be avoided by using two moles of sodium ethoxide to one of malonic ester so that the malonic ester and bromoester, II, would be converted to their ions as rapidly as formed. This is a small help; however, only one molecule of sodium ethoxide will react with a molecule of malonic ester, and the second mole of sodium ethoxide destroys considerable trimethylene dibromide during the early stages of the reaction. These are the difficulties which have caused the low yields previously reported[1], but the dilemma is resolved simply by adding the second mole of sodium ethoxide concurrently with the trimethylene dibromide.

The reality of the principles discussed in the above paragraph is well illustrated by the data in Table I on the yields under various conditions. Runs 1 and 2 are especially striking, since increasing the ratio of sodium (thus converting the third equivalent of malonic ester to its ion) completely reverses the

[1] Since this manuscript was submitted there has appeared a report [Walborsky, *J. Am. Chem. Soc.*, **71**, 2941 (1949)] of preparation of diethyl cyclobutanedicarboxylate by a three-step process from diethyl malonate, the over-all yield being somewhat better than previously reported but considerably less than for the present one-step process.

ratio of cyclic diester to tetraester. Run 3 shows that the relative concentration of trimethylene dibromide has no effect on the ratio of products. It is of interest that the tetraester, V, may be hydrolyzed and decarboxylated to yield pimelic acid, and this would be a favored method of preparing this acid if it were not for its present ready availability from tetrahydropyran (5).

EXPERIMENTAL

Alkylation of diethyl malonate. The diethyl malonate was a redistilled technical product, and the trimethylene dibromide was washed with sulfuric acid and distilled. The ethanol was dried by distillation from sodium. The data in Table I were obtained in runs using 0.25 mole of trimethylene dibromide, and the indicated equivalencies of the other reagents, and 500 ml. of ethanol per mole of sodium. The products were separated by fractionation through a 65-cm. Podbielniak type column containing a tantalum wire spiral and a partial reflux head. The distillation pattern is illustrated by the following data on distillation of the products from Run 1: (a) diethyl malonate, 52.6 g., b.p. 91–92° (15 mm.); (b) intermediate, 2.7 g.; (c) diester, IV, 12.1 g., b.p. 109–110° (15 mm.); (d) intermediate, 2.4 g.; (e) tetraester, V, 46.8 g., b.p. 182–189° (1.5 mm.); (f) residue, about 3.5 g. The best procedure for preparative purposes is described below.

In a three-necked flask equipped with stirrer, reflux condenser protected by calcium chloride tube, and long-stem dropping-funnel, 23 g. (1 atom) of sodium was allowed to react with 500 ml. of dried ethanol. After cooling, 200 ml. of this solution was drawn into the dropping-funnel by suction and this funnel was placed on top of the condenser. There was then added to the flask 96 g. (0.6 mole) of diethyl malonate, this mixture was heated to boiling with stirring, and there was added concurrently during one hour the sodium ethoxide solution and 101 g. (0.5 mole) of trimethylene dibromide. After addition was complete the mixture was heated an additional ninety minutes, then about 400 ml. of ethanol was distilled with continued stirring. The residue was shaken out with water and benzene, and the aqueous phase was extracted with two additional portions of benzene. After removal of benzene, the residue was distilled in a Claisen flask. After a small fore-run, the *cyclic ester* was collected at 105–112° (15 mm.), yield 60–65 g. (60–65%). The small amount of diethyl malonate in this product does not interfere with its use for the preparation of cyclobutanecarboxylic acid.

Cyclobutanecarboxylic acid. The diester was hydrolyzed by heating and stirring under reflux with 1.5 ml. of water and 3 ml. of conc'd hydrochloric acid per gram of ester. The mixture was stirred for one hour after it became homogeneous, usually a total of 3–5 hours. After hydrolysis was complete, water and hydrochloric acid were removed by distillation through a short, indented column and the residue was heated at 160–180° until evolution of carbon dioxide had ceased (usually 1–2 hours). The residue was poured into a distilling flask and distilled at atmospheric pressure, then redistilled at reduced pressure. The yield of colorless *cyclobutanecarboxylic acid*, b.p. 104–106° (21 mm.), is 75–80%. A small additional amount of product may be obtained by ether extraction of the aqueous distillate.

SUMMARY

A method has been developed for obtaining diethyl cyclobutanedicarboxylate in 60% yield, from trimethylene dibromide and diethyl malonate.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

CASHEW NUT SHELL LIQUID. VI. THE OLEFINIC NATURE OF ANACARDIC ACID[1]

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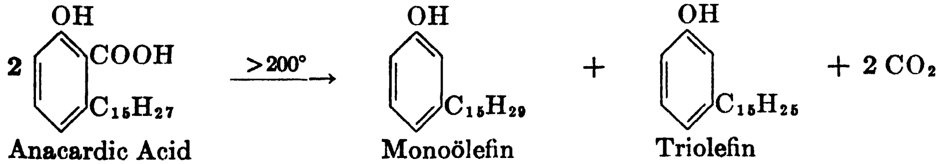
Commercial cashew nut shell liquid is a dark colored indefinite mixture containing three alkenyl phenolic components and certain decomposition and polymerization products. The phenolic components are a monophenol (cardanol),[3] a salicylic acid derivative (anacardic acid), and a resorcinol derivative (cardol) (2).

The monophenol, which is the major component of the commercial shell liquid is formed by decarboxylation of the anacardic acid component during the extraction of the shells at high temperature. The shell liquid when obtained by a low-temperature solvent-extraction process, contains only anacardic acid and cardol. The anacardic acid is the major component.

Although the carbon skeletons of these alkenyl phenols have been definitely established (3), the exact nature of the unsaturation of their fifteen carbon side chain has not yet been determined. Since the industrial uses (4) and the physiological functions (5, 6) of these types of phenolic compounds are intimately associated with their unsaturated character, the problem of clarifying their olefinic structure is one of considerable interest.

The phenolic components of the shell liquid show an unsaturation equivalent to about two olefinic bonds when freshly prepared, and previous investigators have assumed the phenols to be homogeneous diolefins. However, Sletzinger and Dawson (7), working with the monophenolic component of the commercial shell liquid, found that it was not a homogeneous diolefin, but a mixture of mono-, di-, and possibly tri- or higher olefins, having the fortuitous average unsaturation of two olefinic bonds. Qualitatively, the same results were obtained when a sample of the monophenol, resulting from the decarboxylation of a solvent-extracted anacardic acid, was investigated. However, in both cases investigated by Sletzinger and Dawson, the monophenol was subjected to temperatures of 200° or higher during its preparation. It is conceivable that such temperatures may have caused the observed olefinic heterogeneity by disproportionation reactions of the following type on a homogeneous diolefin. Higher olefinic com-



Anacardic Acid — Monoölefin — Triolefin

[1] For the fifth article in this series, see Sletzinger and Dawson, *J. Org. Chem.*, **14**, 849 (1949).

[2] Present address: American Cyanamid Co., Linden, N. J.

[3] The monophenol has also been termed "anacardol". The reasons for preferring the name "cardanol" have been presented elsewhere (1).

ponents in the monophenol could conceivably arise by similar disproportionation reactions involving the monoölefin, triolefin, etc.

For the above reason, it seemed advisable to investigate the olefinic nature of anacardic acid obtained directly from the shells by a low-temperature solvent-extraction process. Consequently, during the investigation every effort was made to use conditions such that disproportionation reactions of the above type could be eliminated from consideration.

METHODS AND DISCUSSION OF RESULTS

In order to obtain anacardic acid from the shells of the cashew nut as close as possible to the form in which it exists naturally in the shell liquids, every precaution was taken during the isolation procedures to avoid temperatures above 100° and prolonged exposure of the anacardic acid to atmospheric oxidation. The same precautions were also observed during all the subsequent work on the olefinic material.

The shells of the nut were crushed and extracted with petroleum ether at the boiling point (60°). The extracted liquid was immediately treated with freshly precipitated lead hydroxide according to the method of Backer and Haack (3) which precipitated anacardic acid as lead anacardate. After decomposing the lead salt by heating with an aqueous solution of *p*-toluenesulfonic acid, the free anacardic acid was completely methylated with diazomethane. The resulting dimethyl-ether-ester, which was used in all of the structural investigations reported in this communication, was a light amber liquid possessing an unsaturation equivalent to 2.10 double bonds. The investigations were carried out using the methylated anacardic acid rather than the free acid to eliminate in large measure the vesicant properties of the free phenol (6), and to protect the phenolic hydroxyl group during oxidative operations on the alkenyl side chain.

Sletzinger and Dawson (7) established the heterogeneous olefinic character of the monophenol fraction of the commercial shell liquid by hydroxylating the olefinic mixture by means of the Prévost reagent, silver iodobenzoate (8), and separating the resulting glycols by fractional crystallization. Oxidative cleavage of a crystalline monoglycol with periodic acid established the position of the double bond in the monoölefinic component of the monophenol as being between carbons 8 and 9 of the fifteen carbon side chain.

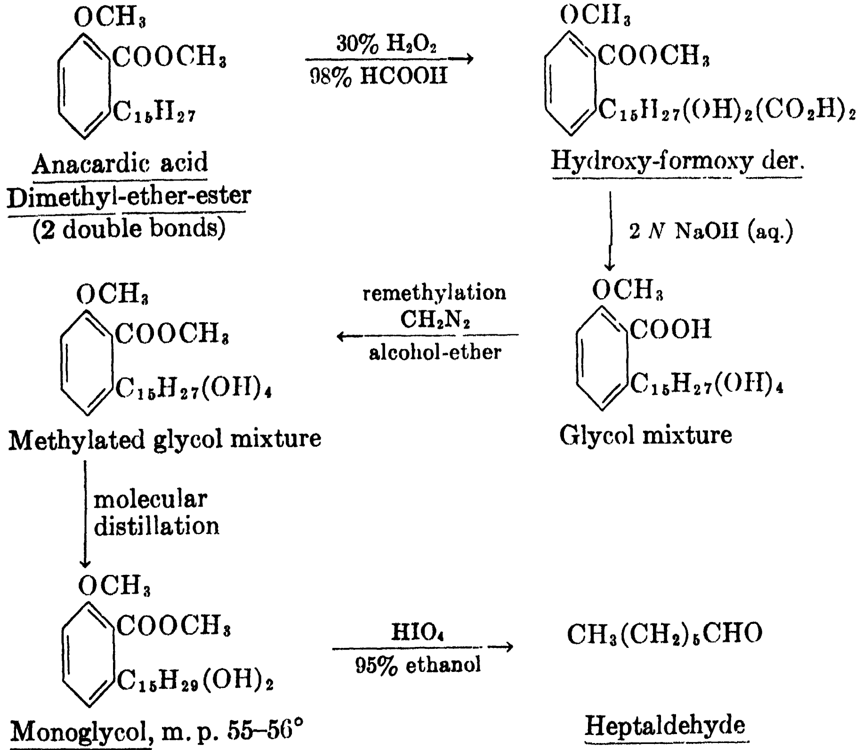
When the Prévost method of hydroxylation was applied to the dimethyl-ether-ester of anacardic acid described above, a mixture of iodinated glycols having the consistency of molasses was obtained. All attempts to obtain a crystalline glycol from the very dark colored mixture failed. Likewise, it was not possible to obtain the corresponding benzoates in crystalline form. The presence of iodine in the aromatic ring was established and this fact rendered unfeasible the separation of the glycols by molecular distillation.

Hydroxylation using the 30% hydrogen peroxide-formic acid reagent described by Swern and co-workers (9, 10) proved more successful in the sense that it was possible by this means to obtain a crystalline monoglycol (See Flow Sheet). The yield of hydroxylated material recovered from the reaction mass, however,

was never in excess of 57% of theory. Some of the loss was probably due to polymerization of the more highly unsaturated olefins in the acid-peroxide reaction mixture. Likewise, it is probable that some of the more highly hydroxylated material was not completely extracted from the reaction mass.

FLOW SHEET

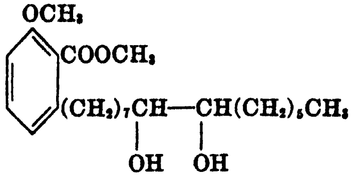
Preparation of Anacardic Acid Dimethyl-ether-ester Glycols



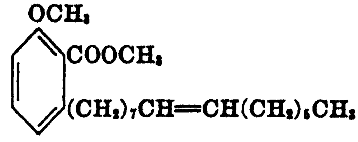
After removal of the solvent, the resulting mixture of glycols was fractionated, using a molecular still, and a fraction was obtained which could be crystallized. The crystalline material melted at 55–56°, and analyzed correctly for the monoglycol of the anacardic acid dimethyl-ether-ester.

Fractions which distilled at higher temperatures, with signs of decomposition, remained liquid even after repeated attempts at crystallization. They were presumably mixtures of monoglycol, diglycols, and decomposition products, for their analyses showed a lower carbon content. A considerable part of the mixture was not distillable and probably consisted of higher glycols.

Cleavage of the crystalline monoglycol with periodic acid yielded *n*-heptaldehyde. These results established the position of the glycol hydroxyl groups as being on carbons 8 and 9 of the fifteen carbon side chain. The corresponding monoölefin was therefore 1-methoxy-2-carbomethoxy-3-(8′-pentadecenyl)benzene.



Monoglycol



Monoölefin

The isolation of a crystalline monoglycol from the dimethyl-ether-ester of anacardic acid, isolated from the shells as described above, clearly establishes that the two double bond unsaturated character of the anacardic acid as it exists in the shell fluids is the result of a mixture of several olefinic components of different degrees of unsaturation. Furthermore, the fact that the monoölefinic component has the same side chain structure as the monoölefinic component of cardanol obtained either from the commercial shell liquid or by decarboxylation of the anacardic acid, demonstrates that the heat processes used in obtaining the commercial liquid and in decarboxylating the anacardic acid do not cause disproportionation of the type suggested earlier. It seems likely, therefore, that the loss in unsaturation observed by previous workers (2, 7), when the various phenolic components of cashew nut shell liquid are subjected to distillation, is due to selective polymerization of the more highly unsaturated components naturally present in the phenols, rather than to the selective polymerization of olefins resulting from disproportionation reactions. It is of interest to note also that such heat processes apparently do not shift the position of the double bond in the monoöolefinic components.

In order to discuss the investigations carried out on the more highly hydroxylated material, it seems advisable to describe the molecular distillation in greater detail. During the molecular distillation at 10^{-5} mm. of several batches of hydroxylated dimethyl-ether-ester of anacardic acid prepared by the use of the formic acid-hydrogen peroxide reagent, it was observed that only about 60% of the material was distillable, and a very small portion of this was a forerun of presumably unhydroxylated material. The second and third fractions (see Table I), distilling between about 125° and 180° and accounting for about two-thirds of the distillable material, were always obtained as a clear, colorless oil which solidified on standing. It was from these combined fractions that the crystalline monoglycol of m.p. 55–56° was obtained in good yield after a single recrystallization. These results would indicate, therefore, that fractions II and III were made up almost completely of monoglycol, and that 40–45% of the sample of hydroxylated material taken for distillation was monoglycol in nature.

Beyond 180° the distillation was accompanied by visible signs of decomposition and the major portion of the fourth fraction (182–223°) actually distilled between 200° and 223°. The distillate was obtained as an amber-colored oil which did not solidify on standing and which could not be crystallized. This fraction, which accounted for about one-third of the distillable material, gave analytical figures for carbon and hydrogen about half-way between the theory for monoglycol and

diglycol. Presumably, it was a mixture of monoglycol, diglycol, and decomposition products.

The residue (about 2.1 g.) which failed to distill at 225°, and which accounted for about 35–40% of the original hydroxylated material, remained as a dark, highly viscous, sticky substance. It presumably contained more highly hydroxylated glycols and decomposition products. Further efforts to resolve this mixture were without success.

It seems likely from the nature of the distillation and the analytical data on the distillate, that fraction IV contained both diglycol and monoglycol and no significant amount of triglycol. When a sample of this fraction was cleaved with lead tetraacetate, formaldehyde was isolated in small amounts as the dimedon

TABLE I

MOLECULAR DISTILLATION AT 10^{-5} MM. OF A 5.4-GRAM SAMPLE OF THE MIXTURE OF GLYCOLS RESULTING FROM THE HYDROXYLATION OF ANACARDIC ACID DIMETHYL ETHER ESTER

FRACTION	TEMP. RANGE (°C.)	APPEARANCE	ANALYSIS[a]	AMOUNT (GRAMS)
I	Forerun up to 126	pale yellow liquid		0.1
II	126–139	white solid	C, 69.66 H, 9.23	0.8
III	139–182	yellowish semi-solid		1.5
IV	182–223	thick amber-colored liquid	C, 67.39 H, 8.86	0.9
Residue	undistillable	black tar		2.1

[a] Sample taken for analysis directly from distillation without further purification. Calc'd for monoglycol $C_{24}H_{40}O_5$: C, 70.55; H, 9.87; Calc'd for diglycol $C_{24}H_{40}O_7$. C, 65.43; H, 9.15.

derivative. No other water-soluble aldehydes were detected, but heptaldehyde arising from the cleavage of the monoglycol was evident from its odor. Since formaldehyde could only result from the cleavage of a glycol occupying the terminal position of the hydroxylated side chain, it may be concluded that fraction IV contained a diglycol component possessing a terminal glycol grouping. As previously pointed out, all attempts to crystallize such a diglycol from fraction IV were without success.

Keeping in mind that only a little over 50% of the original olefinic mixture was recovered in hydroxylated form and that 40–45% of the latter was found to be monoglycol in nature, it may be concluded that at least 20–25% of the original olefinic mixture was monoölefin. To account for the unsaturation equivalent to two double bonds, one must assume, therefore, that the anacardic acid contained appreciable amounts of higher olefins.

SOME CHEMICAL PROPERTIES OF ANACARDIC ACID

All of the hydroxylation experiments discussed above were carried out using completely methylated anacardic acid, for it was observed that the free acid is very sensitive to oxidizing agents. Attempts to hydroxylate the sodium salt with very dilute solutions of $KMnO_4$ at 5–10° resulted only in a black granular substance which was insoluble in water and organic solvents. The free acid is quite stable to oxygen, however, for after ten hours of bubbling oxygen through a benzene solution of the acid at 33° no significant change in the double bond value was observed. The most highly purified sample of the free acid was obtained by chromatographing the dark brown product obtained by the lead precipitation process described earlier. This procedure produced a white waxy solid, m.p. 33–36°, which showed a hydrogenation value of 1.96 double bonds. Anacardic acid forms a lead salt when its alcoholic solution is treated with freshly precipitated lead hydroxide. The lead anacardate thus formed is easily decomposed with sulfuric acid, *p*-toluenesulfonic acid or hydrogen sulfide. If the solid lead anacardate, however, is allowed to stand for a long time (1 year or more) at room temperature, it undergoes a change (presumably polymerization). Attempts to decompose such a salt with one of the above acids produces only a nondescript gum and no anacardic acid.

EXPERIMENTAL

Isolation of anacardic acid. Anacardic acid was obtained from the shells of the cashew nut *Anacardium occidentale*, by solvent extraction and lead precipitation as previously described (3, 1) except for the following modifications. All steps in the procedure were carried out at steam-bath temperatures or lower, and under an atmosphere of nitrogen. The lead precipitations were carried out employing an equimolar quantity of $Pb(OH)_2$ in order to minimize the co-precipitation of cardol. The anacardic acid obtained was a chocolate-colored solid melting at 28–30°.

Anacardic acid dimethyl-ether-ester. A 20-g. sample (0.06 mole) of anacardic acid, prepared as described above, was dissolved in 100 ml. of peroxide-free ether and treated slowly with a cold ether solution of diazomethane (11) until the vigorous evolution of nitrogen had stopped. A small excess of the diazomethane solution was then added and the mixture was allowed to stand for 1 hour at ice-bath temperature.

At the end of this time, a small amount of ether was carefully distilled off in a hood. A greenish-yellow distillate indicated the presence of excess diazomethane and therefore complete methylation. The ether was distilled until the distillate ran colorless (about 50 ml.). The remaining ether solution of the methylated acid was then treated with 4 g. of Darco, refluxed, filtered, and the ether was finally completely removed under a high vacuum. A light amber oil remained in quantitative yield (22 g.).

Anal. Calc'd for $C_{24}H_{38}O_3$: C, 77.37; H, 9.74.

Found: C, 77.58; H, 9.82.

A 2-g. sample of the oil was catalytically hydrogenated using 5% Pd on Darco in ethyl acetate, during which a volume of hydrogen equivalent to 2.1 double bonds was absorbed.

The dimethyl-ether-ester glycols (10). A 9.5-g. sample (0.025 mole) of the dimethyl-ether-ester of anacardic acid (0.05 mole of double bonds) was added to 42 ml. of 95–100% formic acid (m.p. 8°). The two substances did not form a homogeneous mixture; the anacardic acid compound floated to the top. After cooling to about 10°, 7 g. of 29–30% H_2O_2 was added all at once. This amount represents 0.059 mole of potential performic acid. The mixture was then stirred mechanically. After a time lag of about 10 minutes, the reaction rapidly heated up,

reaching a temperature of 70°, and the mixture slowly turned reddish-brown. A cold-water bath was initially used to bring the temperature down to 40°; thereafter, a warm-water bath served to keep the reaction at 40° for four hours during which the reaction mixture was continuously stirred. The mixture on standing separated again into two immiscible phases, the hydroxy-formoxy derivatives of the dimethyl anacardic acid separating on top as a brown oil.

The excess formic acid was distilled off as completely as possible at reduced pressure and at a temperature not exceeding 60°. To the dark brown oily residue was then added 100 ml. of 2 *N* NaOH and the mixture was refluxed for 1½ hours during which the hydroxy-formate and the methyl ester groups were hydrolyzed. Towards the end of this period, a small amount of ethanol was added to produce a homogeneous solution. The alkaline solution was extracted once with ether, to remove polymerized material, and then was carefully acidified with dilute H_2SO_4 to *p*H 4. A very dark brown, viscous oil, which was extracted several times with ethyl acetate, separated.

The ethyl acetate was distilled off thoroughly at reduced pressure, leaving a thick oily residue sparingly soluble in organic solvents such as ether and benzene. To remove unhydroxylated olefinic material, the residue was rapidly washed once with ether. The residual methyl-ether-anacardic acid glycols thus obtained were dissolved in 100 ml. of 95% ethanol and re-methylated at the carboxyl groups by slowly adding an ether solution of diazomethane in slight excess. After standing for two hours, the ether was removed by distillation (hood). The remaining alcohol solution of the glycols was decolorized somewhat by refluxing with Darco and filtering. After the alcohol had been completely removed at reduced pressure, the residue was dried by adding 50 ml. of anhydrous benzene and distilling off the benzene *in vacuo*. The resulting crude mixture of glycols remained as a dark brown, very viscous oil weighing 5.5 g. (50%).

Molecular distillation of the glycols. A 5.4-g. sample of glycols prepared as described above was placed in a small, cylindrically-shaped molecular still having a cold finger extending to within about 1 cm. of the surface of the distilling substance. The distillate, after having condensed on the cold finger, dropped into a 6-tube fraction cutter which could be easily turned by hand. The distillation was carried out at 10^{-5} mm. (mercury vapor pump) while the still was heated by a Variac-controlled electrical heater. The distillation data are summarized in Table I.

From each of the fractions II and III a colorless crystalline monoglycol was obtained in good yield by recrystallization from 60% ethyl alcohol; m.p. 55–56°.

Anal. Calc'd for monoglycol $C_{24}H_{40}O_5$: C, 70.55; H, 9.87.

Found: C, 70.30; H, 9.54.

The crystalline monoglycol was very readily soluble in benzene, ether, alcohol, and chloroform, but insoluble in petroleum ether.

All attempts to obtain a crystalline product from fraction IV proved unsuccessful.

Cleavage of monoglycol with periodic acid (12). A 1.0-g. sample (0.0024 mole) of the monoglycol was dissolved in 60 ml. of aldehyde-free 95% ethanol, and to this solution was added 546 mg. of paraperiodic acid (H_5IO_6, equivalent to 0.0024 mole of HIO_4) dissolved in 5 ml. of water. Some heat was evolved and the solution turned a light yellow color. The reaction mixture was allowed to stand at room temperature for four hours; it was then diluted with twice its volume of water and shaken six or seven times with small portions of ether to extract the ether-soluble aldehydes.

The combined ether extracts were evaporated to a small volume which was added to 100 ml. of hot water and immediately steam-distilled. The distillate (about 200 ml.) was extracted with ether as above and on evaporation yielded a small oily residue which smelled strongly of aldehyde. To the residue was added 250 mg. of 2,4-dinitrophenylhydrazine dissolved in 75 ml. of 95% ethanol, and 1.0 ml. of conc'd HCl. The mixture was refluxed on the steam-bath for 30 minutes. After distilling off about 10 ml. of alcohol, the solution was cooled and 270 mg. of a yellow crystalline 2,4-dinitrophenylhydrazone was obtained. The material was recrystallized to constant melting point (103–104° corr.) using ethyl alcohol acidified

with HCl. Several mixed melting points with an authentic sample of *n*-heptaldehyde 2,4-dinitrophenylhydrazone (m.p. 104–105° corr.) showed no depression.

Anal. Calc'd for $C_{13}H_{18}N_4O_4$: C, 53.06; H, 6.12; N, 19.05.

Found: C, 52.78; H, 5.93; N, 18.84.

In another experiment in which the monoglycol was cleaved with periodic acid as above, the aldehydic residue was treated with 500 mg. of dimedon (5,5-dimethyldihydroresorcinol) in 40 ml. of a 50% aqueous ethanol solution. After heating on the steam-bath two hours, and standing at room temperature for about a day, glistening mica-like flakes settled out on shaking and cooling. During two recrystallizations from 95% alcohol the melting point remained constant (100–101° corr.), and a mixed melting point with an authentic sample of heptaldehyde dimedon derivative (m.p. 102–103° corr.) melted sharply at 101–102°.

Anal. Calc'd for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64.

Found: C, 73.45; H, 10.45 (one recryst.); C, 73.39; H, 10.25 (two recryst.).

Cleavage of higher glycol fraction with lead tetraacetate, (12, 13). Preliminary cleavage experiments with the higher glycol material obtained in fraction IV (Table I) revealed that better yields of formaldehyde could be more easily obtained using lead tetraacetate than with periodic acid as the cleavage agent. In a typical experiment a 0.7-g. sample of fraction IV was dissolved in 50 ml. of glacial acetic acid which had previously been distilled from $KMnO_4$. To this solution was added 1.0 g. of pure lead tetraacetate, which had been recrystallized several times from glacial acetic acid, and the mixture was shaken gently until homogeneous and then allowed to stand at room temperature for 3–4 hours.

The water-soluble aldehydes were then extracted by shaking the reaction mixture several times with small portions of water, during which the solution turned brown due to the hydrolysis of the excess lead tetraacetate. The combined water extracts were then steam-distilled directly into 20 ml. of 95% aldehyde-free ethanol containing 0.5 g. of the dimedon reagent. The dimedon-distillate mixture was heated to 60° for 2 hours and then allowed to stand at room temperature over night. The next day long white needles melting at 186–187° were obtained (yield, 35 mg.). A mixed melting point with an authentic sample of formaldehyde dimedon compound (m.p. 188–189°) showed no depression.

Anal. Calc'd for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27.

Found: C, 69.56; H, 8.38.

Purification of anacardic acid by chromatography. A glass column, 3 ft. long and ¾″ in diameter, was packed to a height of 30″ using 30–35 g. of a 50–50 mixture of Darco and Celite. After washing the column with benzene, a solution of 5 g. of crude anacardic acid (2.10 double bonds) dissolved in 50 ml. of benzene was slowly forced through the column under 5 lbs. of nitrogen pressure. Successive portions of benzene were then passed through the column, and 25-ml. eluate-samples were collected. The first three fractions showed no residue on evaporation of the benzene, but the fourth fraction contained 0.8 g. of a brown oil which did not crystallize on cooling. The next four fractions each contained a small amount of colorless oily liquid (total yield about 2 grams) which solidified to a white, wax-like substance on standing in the refrigerator. Each sample of this material melted at 33–36° and showed an unsaturation equivalent to 1.96 aliphatic double bonds when catalytically hydrogenated using 5% palladium on charcoal in ethyl acetate. After filtering off the catalyst, the solution was evaporated and the white residue without further purification melted at 86–88°, and analyzed correctly for tetrahydroanacardic acid:

Anal. Calc'd for $C_{22}H_{36}O_3$: C, 75.81; H, 10.41.

Found: C, 75.64; H, 10.15.

Acknowledgment. The authors are indebted to the Irvington Varnish and Insulator Company of Irvington, New Jersey, for the supply of cashew nut shell liquid and for their helpful interest in this investigation. The authors also wish to thank Miss Lois May who carried out the microanalyses reported in this communication.

SUMMARY

It has been established that the anacardic acid component of the oil of the shell of the cashew nut *Anacardium occidentale*, is not a homogeneous compound having the structure of a 3-pentadecadienylsalicyclic acid as heretofore believed. The anacardic acid as it occurs naturally in the cashew nut shell and which may be obtained from such shells by cold solvent-extraction, has been found to consist of a mixture of several olefinic components possessing an average unsaturation equivalent to about two double bonds. It has been estimated that at least 25% of the anacardic acid is a monoölefinic component.

Using conditions throughout which would not be expected to alter the olefinic nature of the anacardic acid, the free acid was first methylated with diazomethane and the resulting dimethyl-ether-ester, possessing an average unsaturation equivalent to two double bonds, was hydroxylated using a mixture of 30% hydrogen peroxide-formic acid at low temperatures. The resulting mixture of glycols was partially separated by molecular distillation and a pure monoglycol was obtained.

The crystalline monoglycol on cleavage with periodic acid yielded *n*-heptaldehyde, thereby establishing the monoölefin present in the natural anacardic acid mixture as 1-hydroxy-2-carboxy-3-(8′-pentadecenyl)benzene. The higher-boiling glycol fraction yielded formaldehyde on cleavage with periodic acid or lead tetraacetate, thereby establishing the existence of a terminal olefinic linkage in one or more of the higher olefinic components of anacardic acid.

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[Contribution from the Chemistry Department, Pratt Institute of Science and Technology and the Department of Materia Medica of the Long Island University, Brooklyn College of Pharmacy]

BROMINATIONS CONDUCTED WITH PYRIDINIUM BROMIDE PERBROMIDE

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Previously reported work has indicated that pyridinium bromide perbromide (pyridine hydrobromide perbromide) can be considered a general brominating agent which may be used in brominations ordinarily performed with molecular bromine, such as substitution on aromatic rings and additions to double bonds (1). It is not a specific brominating reagent such as N-bromosuccinimide (2) which is recommended for brominating the allyl position of an olefin. However, the use of peroxide type catalysts (3, 4) and aluminum or zinc chloride (5) have extended the scope of the brominations possible with N-bromosuccinimide. An excellent review of the reactions performed with brominating agents other than pyridinium bromide perbromide has been recently written by Carl Djerassi (6).

Pyridinium bromide perbromide (7, 8) $C_5H_6NBr \cdot Br_2$ is a red crystalline stable salt having the melting point 135–136° (dec.) with previous softening. The reagent has many advantages over dangerous liquid bromine. It is easily handled and stored and may be conveniently weighed. From its structural formula one would suspect that this perbromide can release free bromine, thus when substituted for bromine in any standard bromination the reaction should be expected to proceed in a normal manner. The experiments reported in this paper seem to verify the efficacy of pyridinium bromide perbromide as a substitute for bromine. The quantities of this reagent used were based on the presence of 45% available bromine, although the supplier has indicated 45–50% bromine available.

EXPERIMENTAL

Materials: The pyridinium bromide perbromide (PBPB) used in this study was supplied by Jasons Drug Company of Brooklyn, New York.

6-Bromo-2-naphthol (9). β-Naphthol (36 g., 0.25 mole) and 100 ml. of glacial acetic acid were placed in a 500-ml. round-bottom three-neck flask with a condenser, stirrer, and dropping-funnel. Pyridinium bromide perbromide (178 g.) was dissolved in 100 ml. of hot glacial acetic acid, and this solution was added to the β-naphthol through the dropping-funnel over a period of twenty minutes. The reaction was cooled slightly so as to effect a gentle reflux. The β-naphthol dissolved entirely as the addition took place. Then 25 ml. of water was added to the flask and the entire mixture heated to boiling. After Organic Syntheses (9), 39 g. of mossy tin was added and the mixture was refluxed for two hours. At the end of this period the mixture was cooled to 50° and filtered with suction.

To the filtrate was added 1.5 liters of water. A copious white precipitate formed which was washed three times with divided portions of 250 ml. of water. Upon air-drying the solid, 25 g. of a slightly pinkish powder, m.p. 122–124°, was obtained; yield 45.5%. For the classical

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method using bromine (9), a yield of 53–55 g. (96–100%) is claimed. The sample gave a mixed m.p. 122–123° with material (m.p. 123°) that had been prepared with liquid bromine.

Dibromostyrene (10). Small scale: Pyridinium bromide perbromide (3.4 g.) was dissolved in 3.0 ml. of absolute methyl alcohol and this solution was slowly added to 1.0 g. of styrene; upon cooling crystallization took place. After standing for 15 minutes the crystals were washed several times with absolute methanol. Yield, 1.0 g. (39.5%), m.p. 68.5–69.0°.

The preparation was repeated using glacial acetic acid as the solvent for pyridinium bromide perbromide. Yield, 1.5 g. (59.0%), m.p. 69.5–70.5°.

A similar experiment was carried out using ten times the quantities indicated for the small scale preparation in order to determine relative yields. Yield, 11.5 g. (45.3%), m.p. 71.5–72.0°.

Mixed melting points on all of the above samples with a sample of dibromostyrene (m.p. 71°) prepared with liquid bromine, were 70–71°.

For small scale preparations Cheronis, *et al.* (10) reported a 65% yield of dibromostyrene when bromine was employed.

TABLE I

COMPARATIVE BROMINATIONS

	PYRIDINIUM BROMIDE PERBROMIDE YIELD, %	ELEMENTAL BROMINE YIELD, %
6-Bromo-2-naphthol	45.5	96–100
Dibromostyrene	Small scale 39.5 Large scale 59.0 45.3	Small scale 65.0
2,4,6-Tribromophenol	Small scale 45.5 Large scale 71.0 56.8[a]	Small scale 51.2–56.9
2,4,6-Tribromoaniline	Small scale 29.7 Large scale 24.8	Small scale 49.5–50.4

[a] No potassium bromide present.

2,4,6-Tribromophenol (11). Small scale run, Solution No. 1: Potassium bromide (0.8 g.) was dissolved in 5.0 ml. of boiling water and 1.1 g. of pyridinium bromide perbromide was dissolved in 2.0 ml. of absolute methyl alcohol; the two solutions were mixed. It was found that the potassium bromide solution had to be maintained at an elevated temperature during the addition of the perbromide solution as otherwise the pyridinium bromide perbromide would drop out of solution. Solution No. 2: Phenol (0.1 g.) was dissolved in 1.0 ml. of absolute methyl alcohol and 1.0 ml. of water.

The perbromide-bromide mixture was slowly added to the phenolic solution; during the addition a yellow color was produced. The reaction mixture was permitted to stand for 15 minutes, and 4.0 ml. of water was added. The heavy precipitate which resulted was washed three times with water. The product was dissolved in 2.0 ml. of hot absolute methanol and filtered; cold water was added dropwise until crystallization was complete. Upon air-drying the recrystallized product 0.16 g. (45.5%), m.p. 89°, was isolated. A 51.2–56.9% yield was reported by Cheronis, *et al.* (10).

The preparation was repeated using ten times the quantities indicated for the small scale run; yield, 2.5 g. (71.0%), m.p. 88–88.5°.

Mixed melting points of both products were 89–90° when taken with tribromophenol (m.p. 88–90°) prepared from elemental bromine.

Another preparation was made using the larger quantities, but without potassium bromide. Yield, 2.0 g. (56.8%), m.p. 93–93.5°; mixed m.p. 90–91°.

2,4,6-Tribromoaniline (12). Small scale run: Pyridinium bromide perbromide (1.8 g.) was dissolved in 2.0 ml. of hot glacial acetic acid. To this hot solution was added 0.31 g. of aniline. Intense white fumes resulted. The reaction mixture was permitted to stand for 15 minutes with occasional agitation, and 20 ml. of water was added. Precipitation occurred at this point. The precipitate was washed with cold water, and recrystallized from hot absolute methyl alcohol by the addition of cold water to the hot filtrate. Yield 0.3 g. (29.7%), m.p. 119°. A yield of 49.5–59.4% was reported by Cheronis, *et al.* (11) in a similar experiment.

A large scale preparation was attempted using ten times the quantities indicated in the small scale; yield 2.5 g. (24.8%) m.p. 119–120°.

Mixed melting points of both products were 116–117° using a sample of tribromoaniline (m.p. 118°) prepared from liquid bromine.

The comparative yields obtained with pyridinium bromide perbromide and as reported with elemental bromine are recorded in Table I.

SUMMARY

Pyridinium bromide perbromide, a brominating agent, was substituted for elemental liquid bromine in the bromination of β-naphthol, styrene, aniline, and phenol.

Although no variables were studied the results of the experiments were satisfactory and verified the efficacy of this perbromide as a safe and convenient reagent for performing brominations.

BROOKLYN, NEW YORK

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[Communication No. 1256 from the Kodak Research Laboratories]

DIHYDROINDENONES AND RELATED COMPOUNDS FROM α-ALKYLANHYDROACETONEBENZILS

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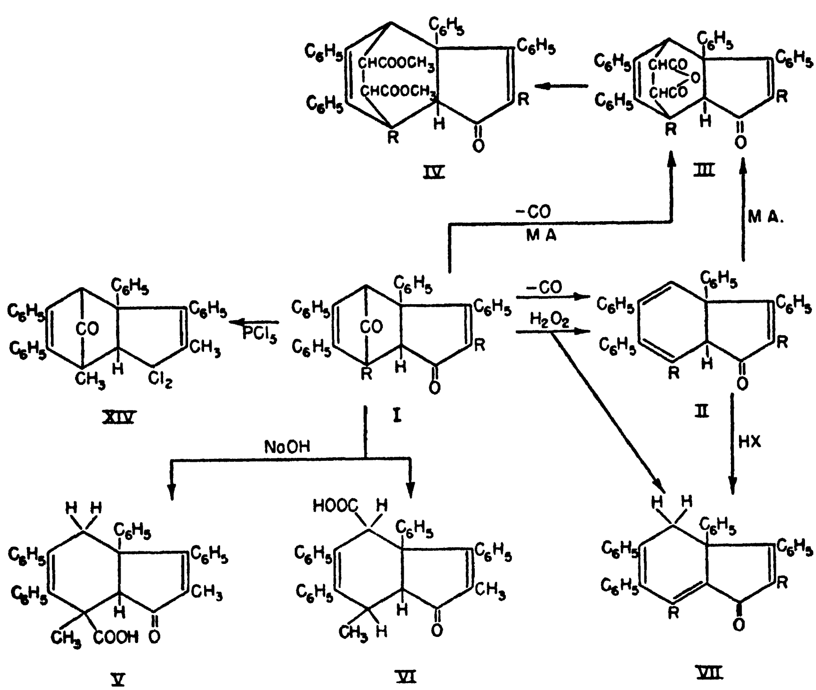
The bimolecular products formed from α-alkylanhydroacetonebenzils (1, 2) behave differently from their homologs, when treated with organometallic compounds (3). Consequently, it was of interest to determine their behavior with other reagents to see whether there are differences, and, if so, whether they are of kind or degree. It has previously been shown (1, 2) that the action of alkaline reagents on all the anhydroacetonebenzils examined is the same. Most of the work described in this paper was done with the dimeric product from α-methylanhydroacetonebenzil, but the *n*-amyl homolog was employed to check certain observations.



The bimolecular products (I) are easily decarbonylated by heating for a short time to dihydroindenones (II), and the latter add maleic anhydride readily; this behavior serves to locate the double bonds. The bridged anhydrides (III) are easily transformed into the corresponding methyl esters (IV). It has been previously shown that the same monoanhydrides (III), along with dianhydrides derived from the monomeric cyclopentadienone, are also formed when the bimolecular products are heated with maleic anhydride at 200° (1).

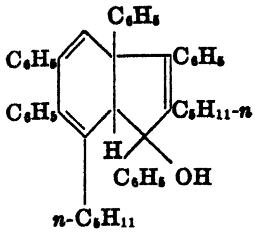
The dihydroindenone (II; R = CH_3) was also obtained when the acid (V) was degraded by oxidation (1). When the bimolecular product itself is treated with alkaline hydrogen peroxide, the same dihydroindenone (II) results, but there is, in addition, about an equal amount of an isomer. The new isomer is no longer capable of adding maleic anhydride. Since it is also formed by the action of hydrogen ion on II, it resembles the unalkylated homolog (4), and is assigned the structure VII. It is assumed that the alkali cleaves the carbonyl bridge to a mixture of acids (V, VI), which are then degraded in the usual manner (1).

When the bimolecular product (I; R = CH_3) is decarbonylated by being heated for a long time, alone or in quinoline, a new isomer (m.p. 168°) of II results. This same substance can also be obtained by similarly heating the isomers (II, VII; R = CH_3); it is, therefore, the end-product of a series of intermediate isomers. The new substance does not add maleic anhydride. When treated quantitatively with methylmagnesium iodide, the new isomer evolves one equivalent of methane but shows no addition; the starting material is recovered upon acidification. It does not give an acetyl derivative with acetic anhydride. When treated with mineral acid or thionyl chloride, it gives an isomer, m.p. 229°, which is a ketone; when the latter is treated with sodium amide, it regenerates the first substance. These two isomers are, thus, related as ketonic and enolic forms.

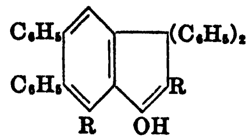
These observations at once recall similar instances (5, 6) in which a keto-enol transformation was noted, the formation of the substances involving the shift of a phenyl group. When such a shift is considered in the case at hand, the apparent discrepancies disappear. Structure IX is assigned to the enol and X to the ketone. There is no evidence that enables one to decide whether, in proceeding from II or VII to IX, there is a single 1,2-shift or two 1,3-shifts of the phenyl group, in the latter case proceeding through an intermediate carbinol (VII). There are analogies for both possibilities, that for the second being perhaps a little better. The driving force is probably the tendency to form an aromatic system.

The behavior of the three isomeric ketones (II, VII, X) with phenylmagnesium bromide is interesting in that the same hydrocarbon results; in no case (when R = CH_3) could an intermediate carbinol be isolated. The hydrocarbon is colorless and does not add maleic anhydride. Obviously there has again been a rearrangement of a phenyl group. By analogy with unalkylated indenones (7) in which it was shown that the tendency was always to give a *gem*-diphenylindene, the structure of the new hydrocarbon is written as shown in XI.

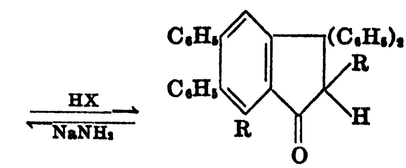
With the amyl homolog (II; R = n-C_5H_{11}), a carbinol (VIII) results. Upon dehydration this gave a hydrocarbon, which was also obtained from the isomer (VII; R = n-C_5H_{11}) without isolation of a carbinol. When the indenone (II; R = n-C_5H_{11}) was treated with p-methoxyphenylmagnesium bromide, an ether corresponding to the hydrocarbon was formed, again without evidence of an intermediate carbinol. All these hydrocarbons (and the ether) undoubtedly have the same type of structure (XI).



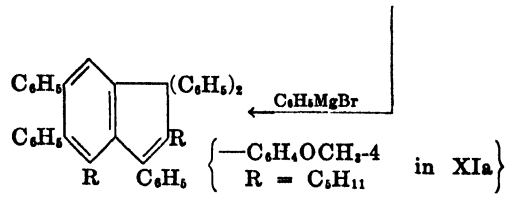
VIII



IX



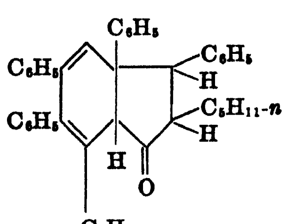
X



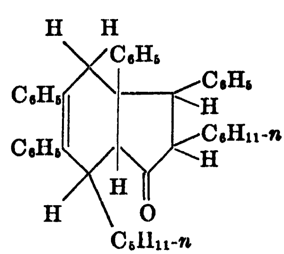
XI

The fact that only 1,2-addition of the Grignard reagents has occurred, rather than both 1,2- and 1,4-additions involving the benzene ring, as was found to take place with the unalkylated homolog (4), is attributed to substitution on the β-carbon of the double bond which forms part of the conjugated system involving the carbonyl group, for it is well known (8) that when several possible positions for addition are available, the one utilized will be the one in which there is the least substitution.

The indenone (II; R = n-C_5H_{11}) was catalytically reduced by hydrogen in the presence of Raney nickel. It gave a dihydro and a tetrahydro derivative; both of these still retained the carbonyl group, for they show one addition but no active hydrogen with methylmagnesium iodide. The dihydro derivative is assigned the structure XII because it was expected that the conjugated system terminating in oxygen would be most easily reduced; in confirmation, it was found to add maleic anhydride. The tetrahydro derivative is represented by XIII, on the assumption that 1,4-addition of hydrogen to the conjugated system in the six-membered ring has taken place. Up to the present, it has not been found possible to add hydrogen to the double bond in this ring bearing phenyl groups (2).



XII



XIII

The bimolecular product (I; R = CH_3) has other reactions. When it is treated with phosphorus pentachloride, one oxygen atom is replaced by two chlorine

atoms. The resulting dichloride (XIV) can be decarbonylated, which shows that the carbonyl bridge is still present. It is concluded, therefore, that it was the indenone oxygen atom that was replaced.

EXPERIMENTAL

The bimolecular products (I) have been previously described (1), as have the maleic anhydride addition products (III). At the time it was thought that a molecule of benzene had been lost in the latter; the calculated analytical values for the various possibilities were so nearly the same that it was impossible to distinguish between them. The molecular-weight determinations were satisfactory if carried out in benzene, but low in carbon tetrachloride (2). From the data which have gradually been collected it is now evident that the previous assumption of the loss of benzene was incorrect.

The bridged esters (IV) were formed by esterifying the anhydrides. A suspension of the latter (5 g.) in 250 ml. of methanol and 15 ml. of concentrated sulfuric acid was refluxed for 20 hours, at which point complete solution was attained. After the addition of 400 ml. of water and after standing in the ice chest, the separated ester was collected and recrystallized from benzene–methanol. The yield of pure ester (IV; R = CH_3) was 3.3 g., m.p. 124°; it contains one molecule of benzene of crystallization. The *amyl* homolog, m.p. 129°, crystallized without solvent.

Anal. Calc'd for $C_{41}H_{36}O_5 \cdot C_6H_6$ (IV; R = CH_3). C, 81.9; H, 6.3.
Found: C, 81.9; H, 6.1.
Calc'd for $C_{49}H_{52}O_5$ (IV; R = n-C_5H_{11}): C, 81.7; H, 7.2.
Found: C, 81.8; H, 6.9.

Oxidation of the bimolecular product by alkaline hydrogen peroxide. A mixture of 5 g. of the bridged compound (I; R = CH_3), 100 ml. of alcohol, 1 ml. of 40% sodium hydroxide, and 10 ml. of 30% hydrogen peroxide was stirred and refluxed for ten hours, cooled, and filtered. The solid (4.5 g.) was fractionally crystallized from acetic acid; the isomer (VII; R = CH_3), m.p. 202°, separated first, while the previously described isomer, 3,3a,5,6-tetraphenyl-2,7-dimethyl-3a,7a-dihydroindenone, m.p. 164°, was isolated from the filtrate. The new isomer, 3,3a,5,6-tetraphenyl-2,7-dimethyl-3a,4-dihydroindenone (VII; R = CH_3), also resulted in a 92% yield when 18.5 g. of the isomer, m.p. 164°, in 85 ml. of hot acetic acid containing 1 ml. of concentrated sulfuric acid was warmed on the steam-bath for two hours. Both isomers show the same red halochromism with concentrated sulfuric acid.

Anal. Calc'd for $C_{35}H_{28}O$: C, 90.5; H, 6.0; mol. wt., 464.
Found: C, 90.7; H, 6.2; mol. wt. (in C_6H_6), 448.

When treated quantitatively with methylmagnesium iodide, it evolved no gas but showed one addition.

The *amyl* homologs (II, VII; R = n-C_5H_{11}) were similarly obtained, and had melting points of 125° (from isopropyl alcohol) and 99–100°, respectively.

Anal. Calc'd for $C_{43}H_{44}O$ (II, R = n-C_5H_{11}): C, 89.5; H, 7.6; mol. wght., 576.
Found: C, 89.3; H, 7.5; mol. wt. (in C_6H_6), 583, 586; one addn.; no act. H.

Action of heat on the bimolecular products (I) *1,1,5,6-tetraphenyl-2,4-dimethyl-3-hydroxyindene (IX) and 3,3a,5,6-tetraphenyl-2,7-dimethyl-3a,7a-dihydroindenone* (II; R = CH_3). When 10 g. of the methylated bimolecular product (I; R = CH_3) was heated for three hours at 240°, and the hot liquid poured into 55 ml. of isopropyl alcohol and allowed to stand, 7.8 g. of IX crystallized. After two recrystallizations from acetic acid, the product had the melting point 168°; it gave a pale lemon-yellow color with concentrated sulfuric acid.

Anal. Calc'd for $C_{35}H_{28}O$: C, 90.5; H, 6.0.
Found: C, 90.4; H, 5.8; 1 act. H, no addn.

This enol is regenerated from the magnesium complex upon acidification. It does not add maleic anhydride.

If the heating was interrupted when the evolution of gas ceased (not over ten minutes), the isomer (VII; R = CH_3) crystallized, under similar treatment, in a yield of 85%; it melted at 164°, and was identical with the previously prepared material (1). It gives a bright red color with concentrated sulfuric acid.

The 168° isomer was also obtained by refluxing substance II or the bimolecular product I (R = CH_3) in quinoline for 70 minutes, or in trichlorobenzene for seven hours, and adding to it 50 ml. of methanol; and by heating substance VII, m.p. 202°, for one-half hour at 240–250°, until the red halochromism changed to yellow.

3,3,5,6-Tetraphenyl-2,7-dimethylindanone (X) was obtained by refluxing for three and one-half hours, a mixture of 6 g. of the enol (IX) and 10 ml. of thionyl chloride, evaporating, and refluxing the residue with methanol. The alcohol was decanted and the insoluble material taken up in chloroform, treated with Norit, filtered, and diluted by an equal volume of methanol. The ketone slowly separated in a yield of 3.2 g.; it was twice recrystallized from *n*-butyl alcohol, then from toluene; m.p. 229°.

Anal. Calc'd for $C_{35}H_{28}O$: C, 90.5; H, 6.0.

Found: C, 90.9; H, 5.7; no act. H; 1 addn.

When a mixture of 0.8 g. of X and 0.5 g. of sodium amide in 10 ml. of cymene was refluxed one-half hour and worked up, 0.4 g. of the enolic isomer (IX) was obtained.

2-Bromo-3,3,5,6-tetraphenyl-2,7-dimethylindanone resulted upon bromination of 1 g. of X in 10 ml. of chloroform; hydrogen bromide was evolved. Methanol was added, and the combined solvents were allowed to evaporate. The residue was then recrystallized from butyl alcohol. The bromoindanone melts at 218° with dec.

Anal. Calc'd for $C_{35}H_{27}BrO$: C, 77.2; H, 5.0.

Found: C, 77.5; H, 5.2.

1,1,3,5,6-Pentaphenyl-2,4-dimethylindene (XI; R = CH_3). To the Grignard reagent prepared from 15.7 g. of bromobenzene and 60 ml. of ether there was added 1.7 g. of the indanone (X) in 30 ml. of benzene, and the ether removed by the usual forcing conditions. After two hours, the reaction mixture was decomposed in the usual manner, and the hydrocarbon recrystallized from acetic acid. It forms nearly colorless crystals, m.p. 218°, that give no color with concentrated sulfuric acid.

Anal. Calc'd for $C_{41}H_{32}$: C, 94.0; H, 6.1; mol. wt., 524.

Found: C, 94.0; H, 6.0; mol. wt. (in C_6H_6), 495.

The same hydrocarbon was likewise obtained by a similar Grignard reaction from the dihydroindenones (II, VII). It does not add maleic anhydride. Efforts to isolate a carbinol by decomposing the reaction products with ammonium chloride were unsuccessful; the hydrocarbon was obtained in each instance. A carbinol was isolated in the amyl series, however.

1,3,3a,5,6-Pentaphenyl-2,7-di-n-amyl-3a,7a-dihydroindenol-1 (VIII) was prepared by a similar procedure; 10 g. of the ketone (II; R = *n*-C_5H_{11}) gave 9 g. of the carbinol (80% yield), m.p. 109°, from alcohol.

Anal. Calc'd for $C_{49}H_{50}O$: C, 90.0; H, 7.6; mol. wt., 654

Found: C, 89.7; H, 7.7; mol. wt. (in C_6H_6), 629.

When the carbinol was warmed in acetic acid containing a drop of sulfuric acid and cooled again, a 72% yield of the hydrocarbon, *1,1,3,5,6-pentaphenyl-2,4-di-n-amylindene* (XI; R = *n*-C_5H_{11}), m.p. 170°, was obtained after recrystallizing from acetic acid.

Anal. Calc'd for $C_{49}H_{48}$: C, 92.5; H, 7.5.

Found: C, 92.1; H, 7.8.

The same hydrocarbon was also obtained from a similar Grignard treatment of the dihydroindenone (VII; R = *n*-C_5H_{11}).

When the dihydroindenone (II; R = *n*-C_5H_{11}) was similarly treated with *p*-methoxyphenylmagnesium bromide, the ether (corresponding to the hydrocarbon) (XIa) resulted; the yield was 74%. After recrystallization from isopropyl alcohol, it melted at 150°.

Anal. Calc'd for $C_{50}H_{50}O$: C, 90.0; H, 7.5.

Found: C, 90.1; H, 7.4.

3,3a,5,6-Tetraphenyl-2,7-di-n-amyl-3a,7a-dihydroindanone (XII) and the corresponding *3a,4,7,7a-tetrahydro* compound (XIII) were obtained by reducing the dihydroindenone (II; R = n-C_5H_{11}) at 4 atmospheres and 70–80°. A mixture of 2 g. of the substance, 0.4 g. of Raney nickel, and 40 ml. of isopropyl alcohol was treated with hydrogen for 15 hours; the gauge dropped 9.5 units. The catalyst was removed by filtration; on chilling, 1.1 g. of the dihydro derivative separated. The filtrate was evaporated to dryness, and the residue crystallized from alcohol; the *tetrahydro* derivative had a melting point of 140°. The *dihydro* compound was recrystallized from acetic acid, after which it had a melting point of 213°.

Anal. Calc'd for $C_{43}H_{46}O$ (A; dihydro): C, 89.3; H, 8.0. For $C_{43}H_{48}O$ (B; tetrahydro): C, 89.0; H, 8.3.

Found: (A) C, 89.4; H, 7.8; no act. H, one addn. (B) C, 88.9; H, 8.3; no act. H; one addn.

SUMMARY

Two homologous series of dihydroindenones have been obtained from the corresponding carbonyl bridge compounds, and their behavior with various reagents has been determined. The reactions parallel those of the lower unalkylated homolog in most respects.

However, the type of indanone having two phenyl groups on one carbon atom, previously obtained only from the bimolecular product, in these series was formed from the bimolecular products *and* from the dihydroindenones. In its behavior it is parallel to a series that was examined earlier. The same hydrocarbon was obtained from all three series.

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[Contribution from E. I. du Pont de Nemours and Co., Inc., Electrochemicals Department, Technical Division]

THE INTERCHANGE REACTION OF VINYL ACETATE WITH ORGANIC ACIDS

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The reaction of vinyl acetate with carboxylic acids in the presence of mercuric salts of strong acids as catalysts to form the vinyl ester of the acid was first reported by Hermann and Haehnel (1) and Toussaint and MacDowell (2).

$$RCOOH + CH_3\overset{\overset{O}{/\!\!/}}{C}OCH{=}CH_2 \xrightarrow{HgSO_4} RCOOCH{=}CH_2 + CH_3COOH$$

This reaction, which we will call the "Vinyl Interchange" Reaction, to differentiate it from typical ester interchange and ester-acid interchange reactions, is a well-known and useful method for the laboratory preparation of many of the simpler vinyl esters. The very mild reaction conditions and the low yields of by-products lead to high yields of monomers of greater purity and activity than those prepared by the reaction of acetylene with acids.

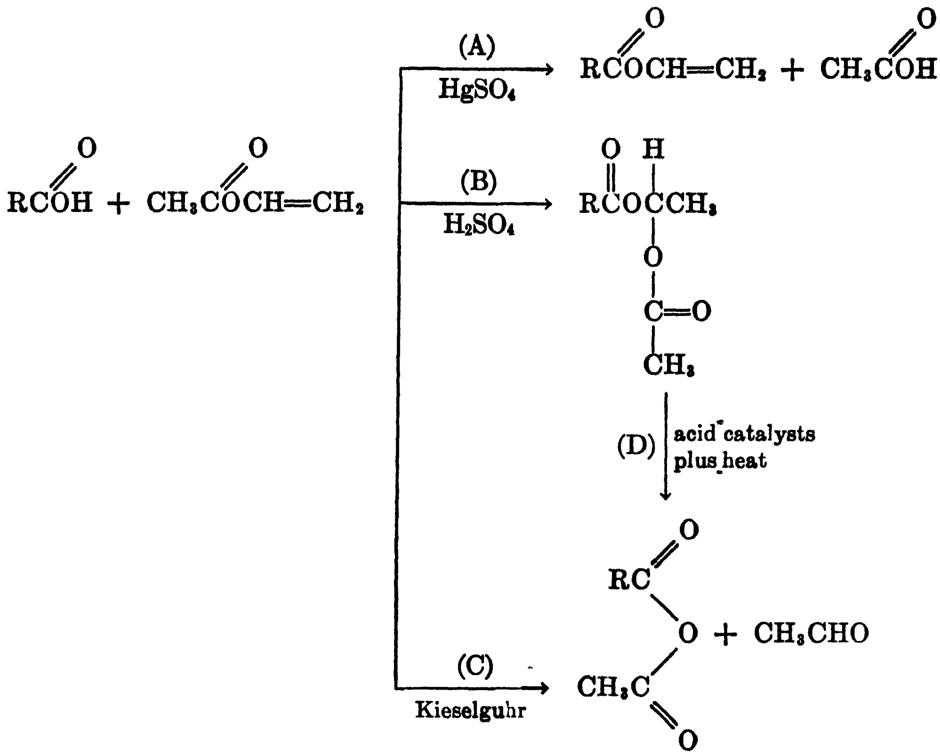
$$RCOOH + HC{\equiv}CH \longrightarrow R\overset{\overset{O}{/\!\!/}}{C}OCH{=}CH_2$$

Furthermore, vinyl esters of dibasic acids are prepared much more easily by vinyl interchange than through the acetylene route, and recent work in this laboratory has shown that the reaction of vinyl acetate catalyzed with mercuric salts is not restricted to carboxylic acids, but will occur with other compounds containing active hydrogen, such as acetoacetic ester and glycolic esters.

There are three major reactions of vinyl acetate with carboxylic acids: (A) the vinyl interchange reaction, which occurs at low temperatures (20–80°) in the liquid phase, (B) the formation of ethylidene diesters at somewhat higher temperatures, generally in the liquid phase with acid catalysts, (3, 4) and (C) the formation of anhydrides of the acids present, in the vapor phase with acid and dehydrating catalysts (5).

Reaction (A), the vinyl interchange reaction, is usually run as described by Toussaint and MacDowell (2). At the same time, ethylidene diester formation (reaction B) occurs significantly under vigorous conditions (75°), especially after long reaction periods. When the formation of the latter occurs, in order to obtain good yields of the vinyl esters, another step is required, the decomposition of the ethylidene diesters to recover the free acids (reaction D) (6). If the reaction temperature is kept at 30° or below, however, the formation of ethylidene diester by-products is generally negligible and high yields of vinyl esters are obtained. This is illustrated in Tables I and II. It is true, however,

that an interchange that proceeds to a final equilibrium value in 1–6 hours at 75° may require 72 hours at 30°.



The reaction is reversible. The higher vinyl esters with acetic acid will all form vinyl acetate under the same experimental conditions as the forward reaction.

In this paper will be presented evidence that the vinyl interchange reaction proceeds through the dissociation of the vinyl acetate, in the presence of mercuric sulfate catalyst, into an acetylene-mercury complex and acetic acid. The acetylene-mercury complex is then capable of reacting with the various acids present to form the vinyl derivatives:

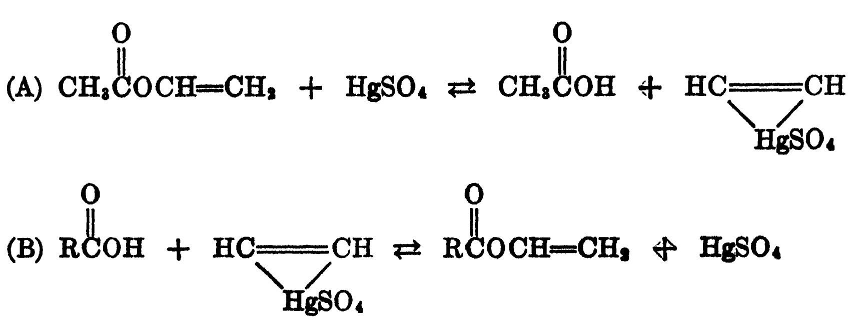


TABLE I

PREPARATION OF VINYL ESTERS BY VINYL INTERCHANGE

VINYL ESTER	REACTION TEMP., °C.	CONVERSION, %[d]	YIELD, %[e]	B.P., °C/MM.	n_D^t	d^{tb}
Stearate	30[a]	62.5	88	169–178/3[c]	1.4423^{30}	0.8517^{40}
	75	49	74	187–188/4.3 (24)	(24)	(24)
Laurate	75	73	93	105/3[f] (23)	$1.4386^{21.5}$	$.8770^{28}$
				142/10 (24)	1.4368^{30}	$.8639^{30}$
					(24)	(24)
Oleate	75	39	82	184–186/3.5	1.4533^{30}	$.869_4^{30}$
				178/2.8 (22)	(22)	(22)
Benzoate	75	71		72–74/3	$1.5259^{21.5}$	1.0706^{28}
				100–101/25 (12, 14)		1.0686^{28}
Trimethyl acetate	30	54	98	110–112	1.4068^{20}	0.873^{25}
	30	80	98			$.885^{20}$
	75	50	70			
Caprylate	30	72.5	95	65–68/3	$1.4271^{22.5}$	$.8898^{29}$
	75	52	83	135/100 (24)	1.4256^{30}	$.8719_4^{30}$
					(24)	(24)
3,5,5-Trimethylhexanoate	75	67	89	85–95/20–26	$1.4226^{21.5}$	
Octyl phthalate	30	71	82	138–142/0.01	1.4979^{21}	1.01^{20}
	75	65	90			
Adipate	75	24	65	102–118/2–3		

[a] 75° for 15 min., followed by 30° for 60 hours. [b] Many of the density measurements were taken by V. Aungier of this laboratory [c] M.p. 30–32° [lit. (24) 35–36°]; anal. 95% vinyl stearate by titration with bromine in acetic acid. [d] Conversion is defined as (100 × $\frac{\text{moles product}}{\text{moles original acid}}$. [e] Yield is defined as 100 × $\frac{\text{moles product}}{\text{moles original acid-moles recovered acid}}$. [f] Anal. 96% vinyl laurate.

Possible intermediate steps include:

$$(A_1)\quad CH_3\overset{\overset{\displaystyle O}{\|}}{C}OCH{=}CH_2 \rightleftarrows CH_3\overset{\overset{\displaystyle O}{\|}}{C}OH + HC{\equiv}CH$$

$$(A_2)\quad HC{\equiv}CH + HgSO_4 \rightleftarrows \underset{\diagdown\;\diagup \atop HgSO_4}{HC{=\!=\!=}CH}$$

$$(B_1)\quad R\overset{\overset{\displaystyle O}{\|}}{C}{-}OH + \underset{\diagdown\;\diagup \atop HgSO_4}{HC{=\!=\!=}CH} \rightleftarrows R\overset{\overset{\displaystyle O}{\|}}{C}OCH{=}CH_2\cdot HgSO_4$$

$$(B_2)\quad R\overset{\overset{\displaystyle O}{\|}}{C}{-}OCH{=}CH_2\cdot HgSO_4 \rightleftarrows R\overset{\overset{\displaystyle O}{\|}}{C}OCH{=}CH_2 + HgSO_4$$

TABLE II

EFFECT OF TEMPERATURE ON BY-PRODUCT FORMATION IN VINYL INTERCHANGE

ACID USED	REACTION TEMP./TIME	CONVERSION TO VINYL ESTER, %	YIELD OF VINYL ESTER, %	CONVERSION TO ETHYLIDENE DIESTER, %
Trimethylacetic acid	75°/6–12 hrs.	50	70	25
	30°/36 hrs.	54	98	<2
Stearic acid	75°/8 hrs.	50	65	26
	75°/15 min. + 30°/60 hrs.	62.5	88	<14

Thus, the reaction must proceed with a breaking of the oxygen-hydrogen bond in the acid, ($R\overset{\displaystyle O}{\overset{\|}{C}}—O \,|\, H$) and a breaking of the oxygen-vinyl carbon bond in the vinyl ester $CH_3\overset{\displaystyle O}{\overset{\|}{C}}—O \,|\, CH{=}CH_2$ [Equation (a) below]. This is contrary to the mechanism of typical ester-acid interchanges [Equation (b)] in which

$$\text{(a)}\quad R\overset{\displaystyle O}{\overset{\|}{C}}—O \,|\, H + CH_3\overset{\displaystyle O}{\overset{\|}{C}}—O \,|\, CH{=}CH_2 \longrightarrow R\overset{\displaystyle O}{\overset{\|}{C}}OCH{=}CH_2 + CH_3\overset{\displaystyle O}{\overset{\|}{C}}OH$$

$$\text{(b)}\quad R\overset{\displaystyle O}{\overset{\|}{C}} \,|\, OH + CH_3\overset{\displaystyle O}{\overset{\|}{C}} \,|\, O—C_2H_5 \longrightarrow R\overset{\displaystyle O}{\overset{\|}{C}}O—C_2H_5 + CH_3\overset{\displaystyle O}{\overset{\|}{C}}OH$$

the carbonyl carbon-to-oxygen bond is broken in the ester, and the carbon-oxygen bond is broken in the acid (7).

Support for this mechanism is found in the following evidence:

(A) *There are marked differences in vinyl interchange reactions as compared to ester interchanges or acid-ester interchanges.* Thus, ester-acid or ester-ester interchanges are catalyzed by acids or bases (although different mechanisms are postulated for the two cases) (7), whereas the vinyl interchange is not catalyzed by either acids or bases (see Table III).[1] Furthermore, the well-known interchange between two different carboxylic acid esters, such as

$$RCOOR' + R''COOR''' \underset{\text{or }(OH^-)}{\overset{(H^+)}{\rightleftarrows}} RCOOR''' + R''COOR'$$

has not been successfully carried out when one of the esters is a vinyl ester.

[1] It is advantageous to use mercuric acetate and sulfuric acid to prepare mercuric sulfate *in situ*, rather than add already prepared mercuric sulfate, as the former leads to a considerably more soluble catalyst.

TABLE III

EFFECT OF VARIOUS CATALYSTS ON THE RATE OF VINYL INTERCHANGE (30°)

CATALYST (0.02 MOLE)	CATALYST SOLUBILITY	EXTENT OF REACTION*, %			REMARKS
		6 Hr.	24 Hr.	104 Hr.	
(a) H_2SO_4	Sol.	0	0	0.2	
" $HgAc_2 + H_2SO_4$	Sol.	96	91	72	
" $PbAc_2 + H_2SO_4$	Insol.		0	0.4	
" Pb	Insol.		0	0	The lead turned white-flaky
" $HgAc_2 + AgNO_3 + H_2SO_4$	Partially Sol.	>96	83	73	
" Dimethylaniline	Sol.		0	0	
" Tetramethylammonium iodide	Insol.		0	0	
" Cuprous chloride (green) hydrate (?) + H_2SO_4	Insol.		0	0.8	
" $FeCl_3$	Sol.		0	0	The high H_2O-sol. acid content due to $FeCl_3$ neutralization alone.
" $MnAc_2 + H_2SO_4$	Insol.		0	0.2	
(b) $CdAc_2 + H_2SO_4$	"	17	21	27	
" $SnAc_2 + H_2SO_4$	"	19		50	
" $HgAc_2 + H_2SO_4$	Sol.	75	90		
" BF_3·Etherate	Sol.			<6	An exothermic reaction does occur at reflux temp. with the formation of ethylidene diesters.

* Extent of reaction measured by total amount of water-soluble acid formed in reaction mixture.

(a) Capric acid (1 mole), vinyl acetate (6 moles), and copper resinate (0.001 mole) made up the reaction mixture. (b) The same as (a), but caprylic acid rather than capric acid was used.

Thus, the attempt to react methyl benzoate and vinyl acetate was unsuccessful,

$$C_6H_5COOCH_3 + CH_3\overset{\overset{\displaystyle O}{\|}}{C}OCH{=}CH_2 \longrightarrow C_6H_5\overset{\overset{\displaystyle O}{\|}}{C}OCH{=}CH_2 + CH_3\overset{\overset{\displaystyle O}{\|}}{C}OCH_3$$

using sulfuric acid, dimethylaniline or mercuric sulfate as catalysts. Further examples of unsuccessful ester-ester interchange with vinyl acetate were with monooctyl phthalate, in which only the free carboxyl group reacted, and the

$$C_6H_4\begin{cases} COOC_8H_{17} \\ COOH \end{cases} + CH_3\overset{\overset{\displaystyle O}{\|}}{C}OCH{=}CH_2 \xrightarrow{HgSO_4} C_6H_4\begin{cases} COOC_8H_{17} \\ COOCH{=}CH_2 \end{cases}$$

ester group was unchanged, and with methyl lactate (8), in which acylation of hydroxyl group occurs with no interchange in basic media, ethyl formate, propyl formate, and acetoacetic ester, although another reaction occurred with the latter which will be discussed more fully in another connection. Many other examples could be mentioned. This can be readily explained by the fact that as ordinary carboxylic acid esters tend to undergo fission at the carbonyl carbon-to-oxygen bond $(\mathrm{R\overset{O}{\overset{\|}{C}}}\,|\,\mathrm{OR})$, with very little tendency to split at the oxygen-to-alcohol-carbon linkage $(\mathrm{R\overset{O}{\overset{\|}{C}}{—}O}\,|\,\mathrm{R})$, an interchange with vinyl acetate (a reaction of an ester with acetylene-mercury complex) proceeds with great difficulty. On the other hand, the oxygen-to-hydrogen bond in carboxylic acids $(\mathrm{R\overset{O}{\overset{\|}{C}}{—}O}\,|\,\mathrm{H})$ is easily broken and so vinyl interchange occurs with the free acids (furthermore, no reaction occurs between acetylene and esters of carboxylic acids under these conditions).

Also, those acids which would undergo acid-catalyzed esterifications or ester interchanges much more slowly than straight chain acids because of steric hinderance, such as trimethylacetic acid and *ortho*-substituted benzoic acids, have no difficulty in undergoing the vinyl interchange because the actual locus of reaction occurs farther away from the interfering groups, being more distant by one oxygen atom. Thus, trimethylacetic acid (pivalic acid), caprylic acid, benzoic acid, and monooctyl phthalate react with vinyl acetate at similar rates under nearly identical conditions.

(B) *A potential mechanism involving the ethylidene diester as an intermediate followed by decomposition to the vinyl ester is unacceptable,* as (a) the vinyl ester

$$\mathrm{RCOOH} + \mathrm{CH_3\overset{O}{\overset{\|}{C}}OCH{=}CH_2} \longrightarrow \left[\begin{array}{c} \mathrm{CH_3\overset{O}{\overset{\|}{C}}O\overset{H}{C}CH_3} \\ | \\ \mathrm{O} \\ | \\ \mathrm{RC{=}O} \end{array}\right] \longrightarrow$$

$$\mathrm{CH_3\overset{O}{\overset{\|}{C}}OH} + \mathrm{R\overset{O}{\overset{\|}{C}}OCH{=}CH_2}$$

interchange reaction is not catalyzed by acids, whereas, the formation of ethylidene diesters is subject to general acid catalysis. An illustration of this point is found in the yields of ethylidene acetobenzoate from equimolar quantities of vinyl acetate and benzoic acid, which are claimed to be quantitative (9).

$$CH_3C(=O)\text{—}OCH\text{=}CH_2 + C_6H_5COOH \xrightarrow{H_2SO_4} CH_3C(=O)OCH(CH_3)(OCOC_6H_5)$$

If the sulfuric acid acted as a vinyl interchange catalyst, some vinyl benzoate, or at least some ethylidene diacetate, should have been found, due to acetic acid formation; whereas, in the presenc of *mercuric sulfate* + acetic acid, vinyl acetate and acrylic acid form mixtures of vinyl esters and ethylidene diesters (10):

$$\underset{\text{vinyl acetate}}{CH_3C(=O)OCH\text{=}CH_2} + \underset{\text{acrylic acid}}{CH_2\text{=}CHC(=O)OH} \xrightarrow[\text{+ HOAc, room temp.}]{HgSO_4}$$

$$\underset{\text{vinyl acrylate}}{CH_2\text{=}CHC(=O)OCH\text{=}CH_2} + \underset{\text{ethylidene diacetate}}{CH_3C(=O)OCH(CH_3)(OCOCH_3)} +$$

$$\underset{\text{ethylidene diacrylate}}{CH_2\text{=}CHC(=O)OCH(CH_3)(OCOCH\text{=}CH_2)} + \underset{\text{ethylidene acetate acrylate}}{CH_3C(=O)OCH(CH_3)(OCOCH\text{=}CH_2)}$$

Here are found all the products expected from the initial formation of vinyl acrylate and acetic acid, due to mercuric sulfate acting as a vinyl interchange

$$CH_3C(=O)OCH\text{=}CH_2 + CH_2\text{=}CHC(=O)OH \xrightarrow{HgSO_4} CH_3C(=O)OH + CH_2\text{=}CHC(=O)OCH\text{=}CH_2$$

catalyst followed by the reaction of carboxylic acids with the vinyl esters present. The acidic substances present act as catalysts to give the observed ethylidene diesters.

(b) The reaction of thiolacetic acid with vinyl acetate proceeds as follows:

$$CH_3C(=O)SH + CH_3C(=O)OC(H)\text{=}CH_2 \xrightarrow{(a)} CH_3C(=O)SCH_2CH_2OC(=O)CH_3$$

$$CH_3C(=O)SCH_2CH_2OC(=O)CH_3 \xrightarrow{(b)} CH_3C(=O)SCH\text{=}CH_2 + CH_3COOH$$

but step (*a*) requires oxygen or peroxides, which are not necessary (or desirable) for the vinyl interchange reaction (which suggests a different mechanism for this step), and step (*b*) occurs only by pyrolysis in the vapor phase at high temperatures (11).

(c) The formation of ethylidene diesters must require a greater energy of activation than the formation of vinyl esters, and so could not possibly act as an intermediate in the vinyl interchange reaction. This is evidenced in the reaction of vinyl acetate with acrylic acid, mentioned above, in which some vinyl acrylate was isolated. This suggests that vinyl acrylate is the intermediate for the ethylidene diester reaction. Furthermore, the conversions to ethylidene diester increase as compared to vinyl ester conversions, at higher temperatures, showing a greater activation energy for the ethylidene diester reaction (See Table II).

(C) *Acetylene plus various hydrogen-active compounds leads to identical products under similar conditions as from vinyl acetate plus these compounds.* Thus, for example, the catalysts for the vinyl interchange reaction are the same as those used for the production of vinyl esters from acetylene and carboxylic acids. Coes first called attention to this fact (10). It should be noted that the proposed mechanism offers the explanation that an acetylene-catalyst complex is the intermediate in both types of reaction. Furthermore, these catalysts, such as mercuric salts of strong acids, will catalyze both types of reactions under similar experimental conditions. Thus, for the reaction of acetylene with trichloroacetic acid in the liquid phase at 50–57° with mercuric phosphate as catalyst, a 25–65% conversion to vinyl trichloroacetate was obtained. Similar results were obtained with chloroisobutyric acid and acetylene. The use of zinc or cadmium salts of the carboxylic acids as catalysts for the acetylene reaction (following the patent of Reppe for stearic or lauric acid), requires higher temperatures (140–190°) (12), and this may correspond to the decreased rate of vinyl interchange when using cadmium or zinc salts as catalysts at 30° (See Table III). Acids and bases are not catalysts for the vinyl interchange reaction any more than they are for the reaction of carboxylic acids with acetylene at low temperatures. Apparently a certain type of coordinate complex of acetylene with mercury is as necessary for vinyl acetate to undergo reactions of this type with carboxylic acids as it is for acetylene itself (13).

Table III indicates that the same catalysts that are active for the production of vinyl esters from carboxylic acids and acetylene are also active for the production of vinyl esters from carboxylic acids and vinyl acetate, that is, mercury, zinc, and cadmium salts.

Furthermore, if this mechanism is correct, it should be possible to react compounds of the general type R—H with vinyl acetate as follows:

$$RH + CH_3\overset{\overset{\displaystyle O}{\|}}{C}OCH{=}CH_2 \xrightarrow{HgSO_4} R\overset{\overset{\displaystyle H}{|}}{C}{=}CH_2 + CH_3COOH$$

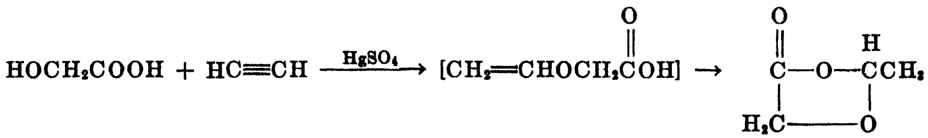
provided the R—H bond is sufficiently labile. Or, looking at the problem from

another point of view, if the R—H bond is sufficiently labile to allow addition of R—H to acetylene under mild conditions, with mercuric sulfate as catalyst,

$$RH + HC\equiv CH \xrightarrow{HgSO_4} R\overset{H}{\overset{|}{C}}{=}CH_2$$

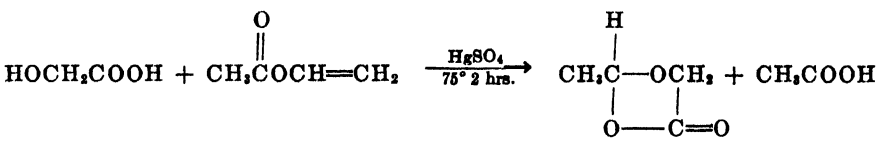
it should be able to undergo the vinyl interchange reaction.

Thus, a cyclic lactide was prepared by Conaway (14) by the addition of glycolic acid to acetylene, probably through the vinyl ether.[2] The catalyst used was mercuric sulfate plus acetic anhydride.

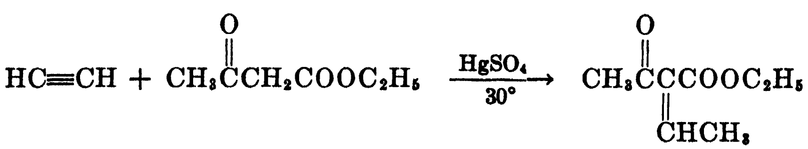


2-methyl-1,3-dioxolone-5
(2-methyl-4 keto-1,3 dioxolane)

This compound was also obtained with glycolic acid and vinyl acetate in over 60% yield.

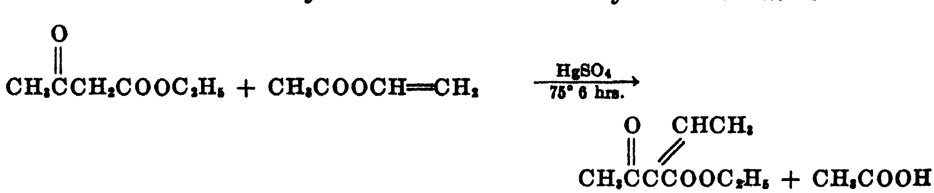


Ethylidene acetoacetic ester has been prepared by the reaction of acetylene with acetoacetic ester.



20—50%

The same product was obtained by the reaction of the methylene group of acetoacetic ester with vinyl acetate to form the ethylidene derivative.



48% conversion

A considerable amount of ethylidene diacetate was also formed due to the vigorous conditions used in this experiment, and this may have helped the reaction proceed by removing one of the products of the primary reaction, that is,

[2] The reactions of alcohols in general with vinyl acetate may be adequately explained by this mechanism, and will be presented in a forthcoming paper.

acetic acid [See reaction (B), described previously]. This is also proof that a carboxyl group is not essential to the mechanism.

The same product is also obtained from the reaction of acetaldehyde and acetoacetic ester. However, the acetylene or vinyl acetate reactions with acetoacetic ester were performed in anhydrous systems, at relatively low temperatures. Very little acetaldehyde forms under these conditions, and hence could not play a major role in the mechanism of the reaction.

Acetaldehyde *bis*-carbomethoxymethyl acetal has been prepared from acetylene and glycolic ester at 25–35° with boron trifluoride-methanol complex as catalyst in 81% yield (15).

$$HC{\equiv}CH + 2HOCH_2COOCH_3 \longrightarrow CH_3\overset{H}{C}{=}(OCH_2COOCH_3)_2$$

And in similar fashion to the other examples, vinyl acetate and glycolic ester, at 35° formed acetaldehyde *bis*-carbomethoxymethylacetal in 57% conversion.

$$2HOCH_2COOCH_3 + CH_3\overset{O}{\overset{\|}{C}}OCH{=}CH_2 \longrightarrow CH_3\overset{H}{C}{=}(OCH_2COOCH_3)_2 + CH_3COOH$$

57% conversion

It has been recently shown that vinyl acetate plus alcohols, in the presence of a mercuric oxide-boron fluoride catalyst, forms acetals (16), and these products and conditions are precisely the same as for acetal formation from acetylene and alcohols (17).[2]

The reaction of another active RH-type compound with vinyl acetate was investigated, namely 1-chloro-1-nitroethane. This compound has a strongly acidic hydrogen, but no vinyl derivative was obtained, and only 2% of polymeric material was isolated.

It has been suggested that the failure of this compound to react in actuality supports the postulated vinyl interchange mechanism, as the hydrogen atom in this nitro compound is labilized only under alkaline conditions.

Similar experiments with propyl formate and ethyl formate indicate that if a vinyl derivative is formed, it is unstable under these conditions, as about 15–20% of a hard, black, brittle polymer was formed.

This mechanism may help to explain the surprisingly small amount of polymer formation during the vinyl interchange reaction, even when run at reflux for many hours with no inhibitor present, for it is known that small amounts of acetylene tend to inhibit vinyl polymerizations.

Attempts to get a chemical test for the presence of free acetylene in solution or vapor phase by precipitating cuprous or silver acetylide have given negative results.

(D) *Substantiation for intermediate steps* A_1, A_2, B_1, B_2, *is considerably more difficult*. However, physical evidence for the existence of an acetylene-catalyst complex, and possibly for step A_1, was suggested from infrared absorption spectra studies.

To summarize our observations of the infrared spectra: (a) weak absorption bands are found in vinyl esters which are near to well-known absorption bands of acetylene; (b) the presence of vinyl interchange catalysts tends to increase the intensity of these acetylene-equivalent absorption bands; (c) vinyl interchange catalysts have effects on the absorption spectra of vinyl esters which are very similar to the action of dissolved acetylene on the absorption spectra.

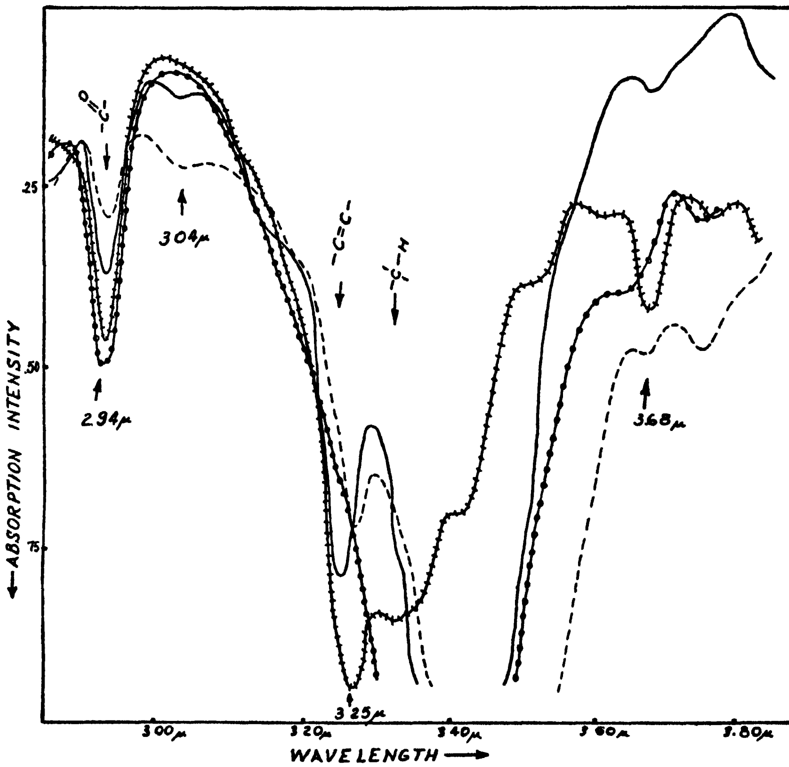


FIG. 1

+++++++	Vinyl acetate
—O—O—O—O—	Ethyl acetate
————————	Vinyl laurate
— — — — —	Vinyl trimethylacetate

It thus appears that the infrared absorption spectra evidence supports the idea that *small amounts of acetylene may be present in all vinyl esters,* and *that the concentration of the acetylene is increased in the presence of a vinyl interchange catalyst, such as mercuric sulfate* (possibly by acetylene-mercury complex formation).

It was realized that attempted identification of absorption bands in vinyl esters specifically due to acetylene would be very difficult because of the significant displacement of a gaseous H—C≡CH absorption band when in a polar solvent. An example of that can be seen in Figure 2, where a sample of vinyl

acetate containing dissolved acetylene gave an absorption (plotted as the reciprocal of the absorption intensity, arbitrary scale, *vs* wave length) specifically due to the addition of acetylene, at 3.14–3.17μ, but which corresponds to the 3.047μ acetylene absorption in the vapor phase. Furthermore, the acetylene-mercury complex may be even more displaced. Nevertheless, certain conclusions are obtainable if these possible displacements are kept in mind.

When infrared spectra of various aliphatic vinyl esters were compared, it was found that they were, of course, quite similar in gross structure, with very

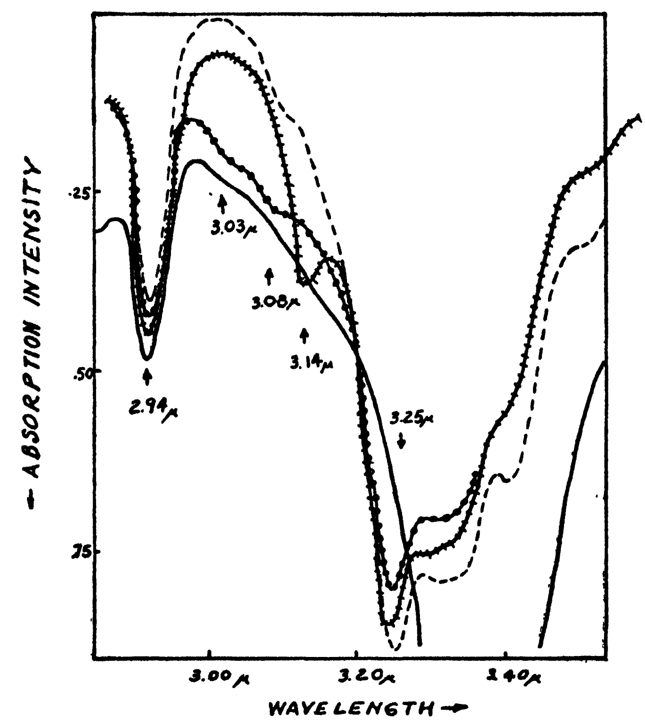


FIG. 2

— — — — —	Vinyl acetate (pure)
+++++++	Vinyl acetate + acetylene
O—O—O—O—O—	Vinyl acetate + catalyst
————	Ethyl acetate + catalyst + .5% acetic acid

large absorptions near 7.8μ due to the C—O—C linkage in the ester group, 5.8μ due to the carbonyl groups, etc. Similarly, when looking at the smaller absorption bands, one, at 2.93 ± 0.02μ, was found to be present in all esters.[3] The magnitude of absorption was found to be proportional to the magnitude of the ester groups as compared to the total molecular weight. For comparison of the spectra of different vinyl esters, the 2.93μ band was superimposed.

[3] This band may be the first harmonic of the carbonyl-in-ester absorption appearing at 5.8μ, and is not to be confused with the band due to hydroxyl groups which may appear in undried or enolizable esters at 2.78± 0.04μ.

Figure 1 shows a comparison of three vinyl esters. At 3.25μ is observed the strong absorption maximum of all vinyl esters, while the very large unresolved absorption near 3.4μ is due to carbon-hydrogen bonds. Other weak absorption bands found only in vinyl esters (as compared to saturated esters) are at 3.70μ, 4.40μ, 5.42μ, 6.15μ, 6.78μ, 7.09μ, 7.70μ, and 13.2μ. (Figures 1, 5 and 6). Also small indications of absorption near 3.04–3.10μ are found in all vinyl esters, with the exception of vinyl acetate (Figure 1), but it was also found in the latter upon the addition of mercuric sulfate (Figure 2).

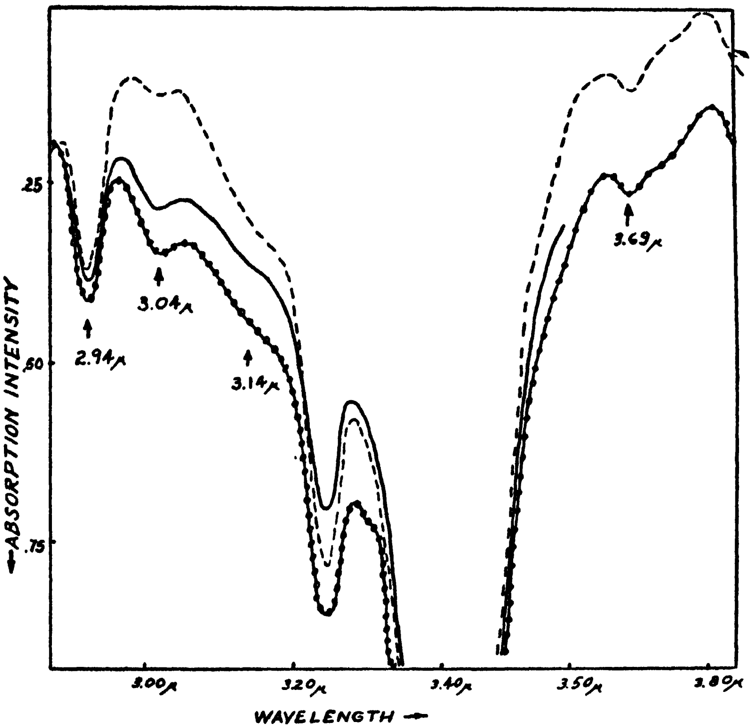


FIG. 3

— — — — — Vinyl trimethylacetate (pure)

O—O—O—O—O— Vinyl trimethylacetate + catalyst

———— Vinyl trimethylacetate + 1% trimethylacetic acid

The above specific absorptions for all vinyl esters are made significant for the present investigation by a comparison with the known absorption maxima for gaseous acetylene. The literature gives values of 2.56μ (weak), (18); 3.047μ (strong), (16); 3.70μ (medium) (16); 4.40μ (medium) (17); 5.11μ (weak) (16); 7.67μ[4] (strong) (19); and 13.7μ (strong) (16), for acetylene gas. An interesting correlation is found in that bands closely situated to *all the significant acetylene absorption bands are weakly present in the vinyl ester spectrum*, except those that are masked by other absorptions of similar wave length. Thus, the carbon

[4] Actually found a doublet at 7.31μ, 7.62μ for acetylene gas.

dioxide-water triplet would mask the 2.56μ band, and possibly the 7.53μ band is masked by the methyl group absorption. This suggests the presence of small amounts of acetylene in vinyl esters (at least in the presence of catalyst).

Furthermore, on the addition of mercuric sulfate catalyst to vinyl acetate, there are some indications of new absorption bands at 3.03μ and 3.10μ, very near to the band of gaseous acetylene (3.047μ), and to the band of acetylene dissolved in vinyl acetate (3.14μ) (Figure 2). That these absorptions of vinyl

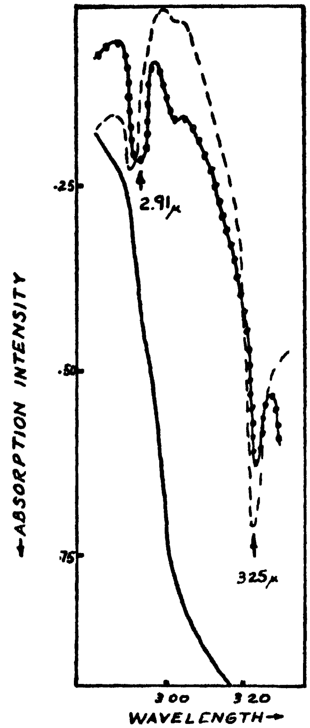


FIG. 4

— — — — — — Vinyl trimethylacetate vapor (over catalyst liquid phase)
O—O—O—O 99% vinyl trimethylacetate + 1% trimethyl acetic acid
———————— 80% vinyl trimethylacetate + 20% trimethylacetic acid

esters in the 3.03–3.10μ range are specific for *vinyl* esters only is also seen on Figure 2, where the spectrum for ethyl acetate plus mercuric sulfate plus acetic acid is shown.[5] The absorption at 3.09μ also increases for vinyl trimethylacetate on the addition of catalyst (Figure 3). It should be noted that this entire region of the spectrum is extensively depressed after catalyst addition to the vinyl ester (and after standing at room temperature for several hours) (Figures 2 and 3). This general depression of the spectrum from approximately 2.95–3.25μ is due to the formation of free carboxyl groups as the catalyzed decomposition

[5] The solutions were filtered clear before spectra were taken.

of the vinyl ester proceeds. This can be seen in a comparison of the pure ethyl acetate spectrum in Figure 1, with the ethyl acetate + catalyst + 0.5% acetic acid spectrum in Figure 2. Also Figures 3 and 4 illustrate the depression of the vinyl trimethylacetate spectrum on the addition of 1% and 20% trimethylacetic acid. The spectrum of ethyl acetate, catalyst, and acetic acid, (Figure 2), shows, however, that the acid formed does not cause the observable absorption in the 3.03–3.10μ region, but in large amounts actually obliterates any indication of minute absorption bands in this region (Figure 4).

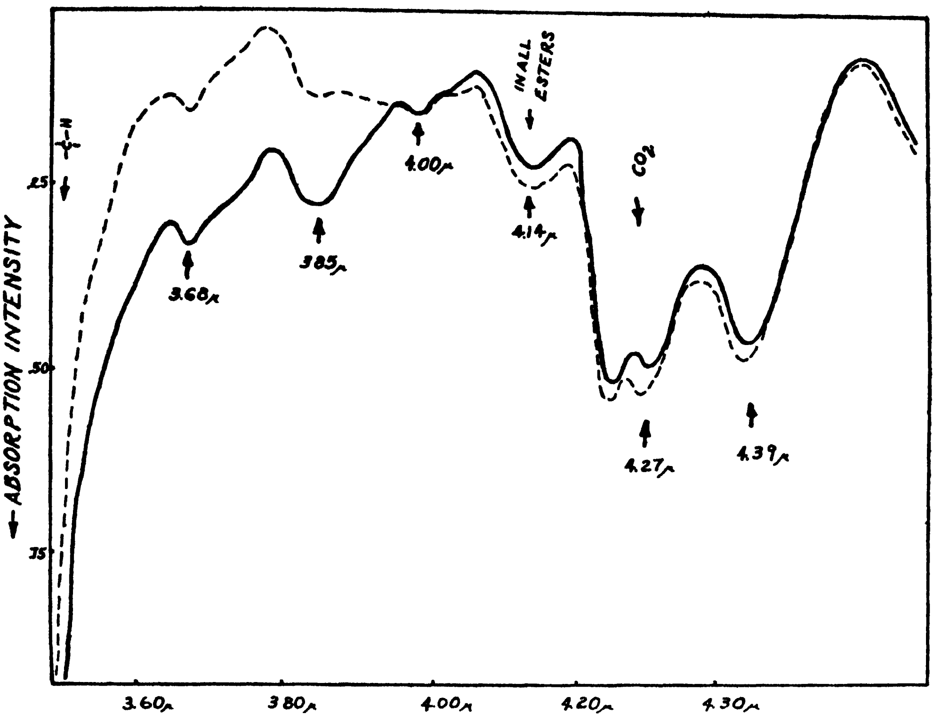


Fig. 5

– – – – – – Vinyl trimethylacetate pure, liquid phase

———— Vinyl trimethylacetate + catalyst

Similar results are obtained in other parts of the spectrum. Thus, the solution of acetylene in vinyl acetate resulted in a general increase of absorption of the vinyl acetate spectrum from approximately 3.6μ to 4.05μ, with maxima at 3.70μ and 3.87μ (Figure 6). On the other hand, the addition of vinyl interchange catalyst (mercuric sulfate) to vinyl trimethylacetate led to almost precisely the same result (Figure 5).

Studies were also made in the vapor phase, in which the spectra of pure vinyl trimethylacetate vapor were compared with the spectra of the gases collected over liquid vinyl trimethylacetate plus mercuric sulfate catalyst (Figure 7).

The catalyzed liquid had been placed in a sealed chamber for 3 weeks, after which time the gas in the chamber was pulled into a 1-meter cell and the spectrum taken. Although the concentrations of the two samples are not exactly equivalent, yet it is clear that a much greater absorption at 3.70μ has developed in the vapor standing over the catalyzed liquid. As this corresponds to the 3.70μ acetylene absorption band, and a titration of the residual liquid indicated a large increase in acid content (18% based on trimethylacetic acid), intermediate steps A_1 and A_2 may be added to our postulated mechanism of the reac-

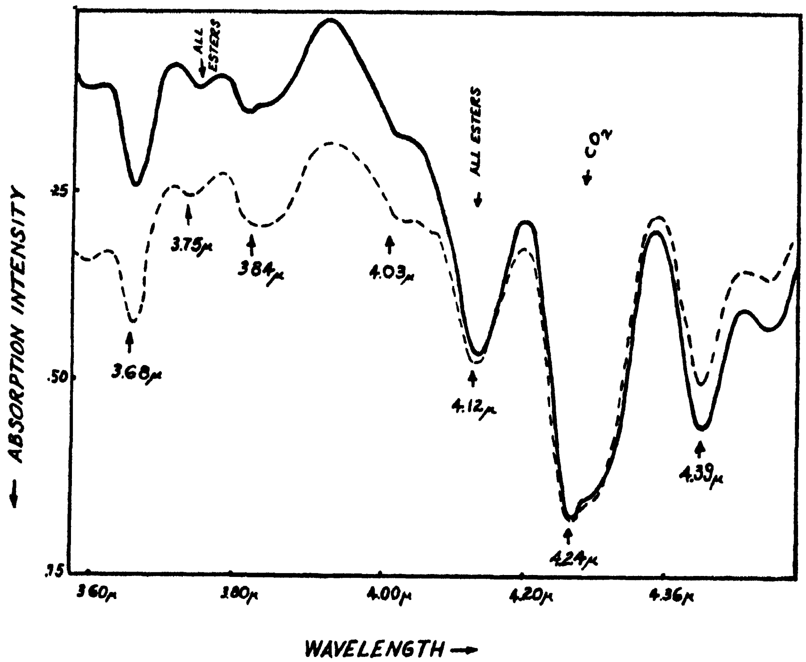


FIG. 6

———————— Vinyl acetate (pure)

— — — — — — Vinyl acetate + acetylene

tion. However, the fact that no correspondingly significant increase in absorption occurred at 3.04–3.19μ (the largest known acetylene absorption), and that acetaldehyde vapor also has a strong absorption at 3.67–3.70μ makes these final observations rather tentative.

It is very desirable that other types of investigation be carried out, such as the use of the heavy oxygen isotope in the carboxylic acid ($R\overset{\overset{O}{\|}}{C}—O^{18}H$) to further prove the permanency of the $C—O^{18}$ bond in the acid during the vinyl interchange. However, it is believed that the evidence thus far collected furnishes strong support for the mechanism of the reaction as described.

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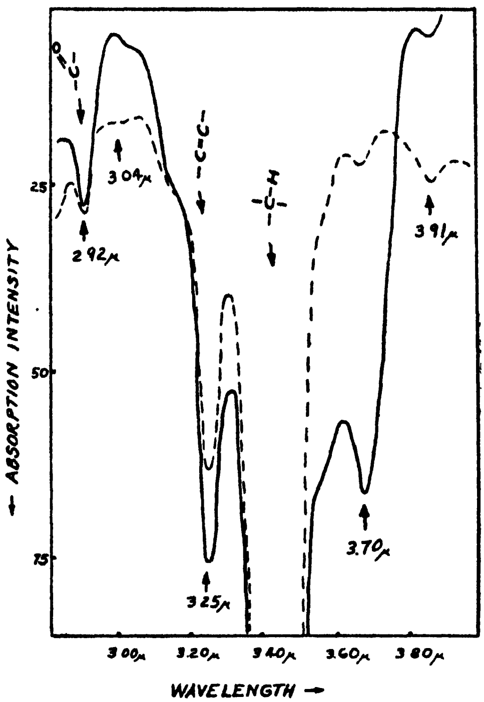

FIG. 7

— — — — — — Vinyl trimethylacetate vapor phase

———————— Vinyl trimethylacetate, vapor phase, over catalyst in liquid phase for three weeks

EXPERIMENTAL

Starting materials. The starting materials were distilled through a three-foot column packed with a glass helices, with the exception of the lauric and stearic acids. These were commercial Armour "Neo Fats" (No. 11, 1-65) and were used directly.

THE VINYL INTERCHANGE REACTION

The vinyl interchange reaction is the procedure similar to that described by Toussaint and McDowell (2) with the following additional observations:

(a) For yields of vinyl esters, it is essential to keep the temperature low (20–30°). This eliminates the formation of ethylidene diesters.

(b) When the reaction is run at low temperatures, a sufficient reaction time must be permitted to allow good conversions (see Table II).

(c) The extent of reaction was followed by removing a small aliquot, extracting it well with ice-water, and titrating the water extracts with standard alkali for acetic acid. As

the extent of by-product formation is small, the determination of acetic acid concentration is a good measure of the conversion to vinyl ester.

(d) The addition of sodium acetate completely stops the reaction. Thus, in a typical reaction mixture of vinyl acetate, trimethylacetic acid, mercuric acetate, and sulfuric acid, a batch that had reached 67% of the final acetic acid concentration was treated with 3% (by weight of acid) sodium acetate. No further change in acetic acid concentration occurred.

(e) The mercuric salt of a strong acid is essential for high catalyst activity. Thus, on mixing trimethylacetic acid and a 6-fold molar excess of vinyl acetate at room temperature, the reaction proceeded at a rate of 3% conversion in the first five minutes with mercuric acetate alone. On addition of 3% mercuric acetate and sulfuric acid (based on trimethylacetic acid) to an identical mixture as above, the salt dissolved, and the reaction proceeded at a rate of 15% conversion in the first five minutes (Table III also demonstrates that sulfuric acid without any mercuric acetate has no catalytic activity whatsoever).

An illustration of the technique to be used in running a low-temperature vinyl interchange reaction is demonstrated for vinyl caprylate. The reagents are added to a 5-liter glass balloon flask in the following order: caprylic acid (b.p. 108–109°/0.5 mm.; 5 moles, 720 g.), vinyl acetate (30 moles, 2580 g.), copper resinate (0.5 g.), mercuric acetate (2% of carboxylic acid, 14 g.), and sulfuric acid (0.5% of acid, 3.6 g). The mixture was vigorously stirred before and after the addition of the sulfuric acid, and after a homogeneous solution resulted, the solution was allowed to stand at room temperature (30°). Five-ml. samples were withdrawn at intervals to see the extent of reaction.

The analyses were run as follows: a 5-ml. sample was shaken with 50 cc. of ice-water. Then 20 ml. of vinyl acetate was added and the mixture was shaken again. The mixture was allowed to stand for 10 minutes until the layers were well separated and clear. The water layer was run off, ice was added, and the cold aqueous layer titrated to the phenolphthalein end point with standard NaOH solution.

After 1.5 hours, the reaction had gone 57% to completion; after 72 hours, the reaction had reached a steady state (calculated over 90% conversion). Ten grams of sodium acetate was added, with good stirring, and the mixture was then heated to 40–45° under water-pump vacuum to remove most of the excess vinyl acetate and the acetic acid that was formed. When the pressure in the system had dropped to about 20 mm., the residue was distilled rapidly under more reduced pressures through a small 1-ft. packed column. The fractions were as follows:

(a) 20 g., b.p. 45–65°/3 mm.
(b) 710 g., b.p. 65–75°/3–5 mm.
(c) 40 g., b.p. 76–105°/3 mm.
(d) 80 g., b.p. 105–112°/3–4 mm.
(e) 40 g., holdup and residue.

Analyses of (e) indicated 20% holdup, 25% water-soluble salts, 55% higher ethylidene diesters, and polymer. Analysis of (d) indicated 86% caprylic acid (by NaOH titration in methanol-water mixtures) and 15% vinyl caprylate (by Br_2 titration in glacial acetic acid-methanol mixtures). Fraction (b) was redistilled. The fractions obtained were:

(b_1) 10 g., b.p. 55–65°/3 mm.
(b_2) 630 g., b.p. 65–68°/3 mm.
(b_3) 15 g., b.p. 68–105°/3 mm.
(b_4) 45 g., b.p. 106°/3 mm.
(b_5) 10 g., holdup and residue.

Fraction (b_2) was pure vinyl caprylate; (b_3) and (b_2) had increasingly larger percentages of caprylic acid over vinyl caprylate.

The conversion to actually obtained pure product, even with a very inefficient column, was 72.5%. At any rate, only 40 g. of material was lost, resulting in a yield of 95% based on recoverable materials.

Reaction of vinyl acetate with glycolic acid. One mole (76 g.) of glycolic acid, 6 moles

(516 g.) of vinyl acetate, and 0.9 g. of sulfuric acid were mixed together at 30°; a homogeneous solution resulted. The solution was heated to reflux (75°) with stirring for two hours, cooled to 30°, and 5 g. of sodium acetate added, with stirring. The mixture was distilled directly and 65 g. (64% conversion) of 2 methyl-1,3-dioxolone-5 (2-methyl-4-keto-1,3-dioxolane) was obtained. B.p., 78–83°/45–54 mm., neutral equiv., 104 (theory, 101); d^{20} 1.11, decomposes in water after a few seconds. Tests for unsaturation were negative. These physical constants compare well with the product obtained from acetylene and glycolic acid (14).

Reaction of vinyl acetate with acetoacetic ester. Two moles (260 g.) of ethyl acetoacetate (b.p. 57°/3 mm., n_D^{25} 1.4200), 12 moles (1032 g.) of vinyl acetate (b.p. 72°), copper resinate (0.1 g.), 5.2 g. (2%) of mercuric acetate, and 2.6 g. (1%) of sulfuric acid were mixed in the above order and the reaction solution was heated to reflux with stirring for 22 hours. Sodium acetate (6 g.) was added with stirring, and the excess vinyl acetate and acetic acid were removed by a water pump. The liquid residue was fractionated under reduced pressure, and the following fractions were obtained:

(a) 153 g., b.p. 45–60°/4 mm. n_D^{23} 1.4082
(b) 104 g., b.p. 60–73°/4–3 mm. n_D^{23} 1.4302
(c) 148 g., b.p. 74–76°/3 mm. n_D^{27} 1.4482, d^{20} 1.0272
(d) 78 g., residue and holdup.

Fraction (a) was a mixture of ethyl acetoacetate and ethylidene diacetate. Fraction (c) was ethylidene acetoacetic ester (48% conversion), which gave positive tests for unsaturation with bromine in carbon tetrachloride, and compared well with the product prepared from acetylene and acetoacetic ester (see below).

The product prepared from acetaldehyde and acetoacetic ester had the following physical constants: b.p. 101°/15 mm., n_D^{17} 1.4526, d_4^{17} 1.026. (21) *Anal.* C, 61.20; H, 7.79 (21).

Reaction of acetylene and acetoacetic ester (previously carried out by Conaway). Acetylene (1 mole) was added to 1 mole of the ester in the presence of 2% mercuric sulfate. The reaction temperature was kept below 40° to prevent considerable resinification. The products were filtered and distilled at 2 mm. Yield, 37 grams (20%) of ethyl α-ethylideneacetoacetate; a colorless liquid, with a sharp pungent odor, b.p. 90°/10 mm., d_4^{25} 1.0158, n_D^{25} 1.4510,

Anal. Calc'd: C, 61.54; H, 7.69.
Found: C, 61.36; H, 7.91.

Reaction of vinyl acetate with methyl glycolate. One mole (90 g.) of methyl glycolate (b.p. 71°/41 mm., n_D^{20} 1.4147), 6 moles (516 g.) of vinyl acetate, 0.001 g. of copper resinate, and 1.8 g. of reagent-grade mercuric sulfate were added in the above order to a 3-necked flask with good stirring at 35°. An exothermic rection occurred, which raised the internal temperature to 39° (bath temp. 36°) over a period of 30 min. When the heat evolution ceased the reaction solution was stirred at 40° for 2 hours, at which time the solution analyzed 0.6 mole of acetic acid. Five grams of sodium acetate were added, stirring was continued for 5 minutes, and the mixture then was distilled at reduced pressure through a 1-foot packed column.

(a) cold trap, 503 g., b.p. less than 45°/4 mm.
(b) 16 g., b.p. 45–55°/4 mm. (methyl glycolate)
(c) 10 g., b.p. 56–109°/2 mm.
(d) 67 g., b.p. 109–112°/2 mm., n_D^{22} 1.4297.
57% conversion, at least 70% yield of acetaldehyde *bis*- methylglycolate acetal.
(e) 5 grams, residue and holdup.

The reaction of acetylene with methyl glycolate is described by Coffman (15).

The reaction of vinyl acetate with 1-chloro-1-nitroethane. One-half mole (55 g.) of 1-chloro-1-nitroethane (b.p. 125–126° neutral equivalent 113), 3 moles (258 g.) of vinyl acetate, 2.2 g. of mercuric acetate, 0.1 g. of copper resinate, and 1.1 g. of sulfuric acid were added in the above order. The solution was heated to reflux with stirring for 7 hours. Five g. of sodium acetate was added, and the mixture distilled at atmospheric pressure through a 3-foot packed column. After the vinyl acetate was removed, the temperature rose imme-

diately to 120–128°, and 57 g. of chloronitroethane was recovered. A residue of 7 g., which was hard, black, and brittle, remained in the distilling flask.

The reaction of vinyl acetate with n-propyl formate. Two moles (176 g.) of *n*-propyl formate (bp. 78–80°), 12 moles (1032 g.) of vinyl acetate, 0.2 g. of copper resinate, 5.2 g. of mercuric acetate, and 2 g. of sulfuric acid were mixed with stirring. The solution was then heated to reflux with stirring for 7 hours, 6 g. of sodium acetate was added, and the mixture distilled at 750 mm.

(a) b.p. 70–75°, 1074 g. (mainly vinyl acetate)

(b) b.p. 75–85°, 26 g.

(c) b.p. 85–128°, 3 g.

(d) b.p. 128–131°, 16 g., low unsaturation test, slowly decomposes in water, turned black on standing. After an attempted water wash the product boiled over a 100–135° range.

(e) 37 g., black brittle residue.

Chemical tests for the presence of free acetylene in solution. Negative results were obtained with the following procedures: A very slow stream of nitrogen was passed through a catalyzed sample of vinyl caprylate at room temperature and the issuing stream passed through a solution of the Ilosvay and Schultz reagent for acetylene (20) ($CuSO_4 + NH_3 + NH_2OH \cdot HCl$ + gelatin, which gives a reddish-brown dispersion with acetylene). This sensitive but unstable reagent tended to break down after several days, and a blue-green precipitate of copper hydroxide was observed. Negative results were also obtained with a test solution of silver nitrate in ethanol or ethylene glycol. At higher temperatures (60°), a small amount of acetaldehyde (1 g.) was evolved from 220 g. of vinyl caprylate over 36 hours, and also an increase in the acid content of the residues occurred. This suggests that a reaction similar to (C) is occurring under these conditions to a small extent.

Infrared spectra measurements. The vinyl esters were all redistilled for this work.

The instrument was a Perkin-Elmer Infrared Spectrometer, Model 12B, containing a sodium chloride prism. In general, a 0.05 mm. slit and sealed cells 5 mils thick were used in order to study the liquid samples. Room temperature was not controlled, and so slight variations (0.02 μ) in displacement of spectra were observed from time to time. Thus, for purposes of comparison in this work, the spectra were superimposed on reference bands, rather than compared on a basis of instrument calibration of drum reading *vs.* wave length.

To calibrate the instrument in the region under investigation, reference points used were the 2.67μ and 2.76μ water vapor bands, the 3.05μ of acetylene, the 4.23μ and 4.28 doublet for carbon dioxide, and 5.76μ and 7.042μ of water vapor.

The instrument is sensitive enough to determine quantitatively acetylene in the gas phase at a concentration of 0.1% (10 cm. cell).

SUMMARY

1. In the interchange reaction of vinyl acetate with carboxylic acids to form the vinyl ester of the carboxylic acids, (called the vinyl interchange reaction) it is found that at lower temperatures (30°) the formation of the major by-products, ethylidene diesters, is almost completely eliminated.

2. A mechanism for the vinyl interchange reaction is presented, which accounts satisfactorily for all of the characteristics of the reaction. The mechanism involves the dissociation of the vinyl ester, in the presence of catalyst, into the free carboxylic acid and an acetylene-catalyst complex. Considerable chemical and physical evidence is presented in support of the mechanism.

3. The above chemical evidence includes several new reactions of vinyl acetate. The new reactions of vinyl acetate are with glycolic acid, methyl glycolate,

and acetoacetic ester. Two new vinyl esters, vinyl 3,5,5-trimethylhexanoate and vinyl octylphthalate, were also prepared.

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[Contribution from the Sterling Chemistry Laboratory, the Bingham Oceanographic Laboratory, and the Bermuda Biological Station for Research]

CONTRIBUTIONS TO THE STUDY OF MARINE PRODUCTS. XXIII.[1] STEROLS FROM SPONGES OF THE FAMILY *HALICLONIDAE*

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In the XIXth communication of this series (1), the isolation of chalinasterol from the sponge, *Chalina arbuscula*, has been described, and in a subsequent paper the suggestion has been made that this sterol is identical with ostreasterol (2). Since then, Dr. de Laubenfels,[3] the eminent sponge taxonomist, has informed the senior author that the name of this sponge should be changed to *Haliclona arbuscula*, because more recent taxonomic studies have shown the sponge to be a typical representative of the family *Haliclonidae*, genus *Haliclona*. Approximately one hundred species have so far been placed within this genus, the taxonomy of which is not always lucid. It appeared, therefore, of interest to ascertain whether the presence of chalinasterol is sufficiently characteristic for certain studies. For this reason the sterols of six other species of *Haliclona* have been investigated. The sponges have been collected by the senior author in the waters near Bermuda and Florida,[4] and they have been identified by Dr. M. W. de Laubenfels. The contents of the fatty material of these sponges are shown in Table I.

I. *Haliclona variabilis* (Dendy) de Laubenfels. This sponge is fairly common in the shallow waters of the Bermuda Archipelago, particularly in Harington Sound and Walsingham Pond. After only a few recrystallizations, the acetate of its sterol showed the constant melting point 147–148°; $[\alpha]_D^{26}$ −52°. Its identity with poriferasteryl acetate (3) was demonstrated by comparison with an authentic sample, and by its conversion to the high-melting tetrabromide, and to poriferasterol, m.p. 155.5–156°; $[\alpha]_D^{26}$ −50°. It is estimated that poriferasterol represents in excess of 80% of the original sterol mixture. This sponge therefore affords the richest source of poriferasterol which has so far been encountered.

II. *Haliclona permollis* (Bowerbank) de Laubenfels. This soft, compressible, purple sponge was collected in Hungry Bay, Bermuda. The acetate of the crude sterol obtained from this sponge melted at 133–135°; $[\alpha]_D^{26}$ −46°. Fractionation of the bromine addition products led to the isolation of a high-melting tetrabromide, which upon debromination yielded poriferasteryl acetate.

[1] Communication XXII of this series will appear in *J. Marine Research Sears Foundation*, **8**, 97 (1949).

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[4] The authors are greatly indebted to Dr. D. F. Brown, Bermuda Biological Station for Research, and Dr. W. F. Smith, University of Miami, for their generous assistance in the collection of material.

Debromination of the more soluble bromides yielded an acetate, m.p. 135–136°; $[\alpha]_D^{26}$ −38°, which appeared to be clionasteryl acetate. Lack of material prevented a more detailed separation of the components of the sterol mixture, but there appears little doubt that poriferasterol and clionasterol are the major constituents.

III. *Haliclona coerulescens* (Topsent). This light blue sponge was collected on Featherbed Bank near Miami. The acetate of the crude sterol obtained from this sponge melted at 133°; $[\alpha]_D^{26}$ −40°. Fractionation by way of the bromides gave results similar to those described under *Haliclona permollis*. It is estimated that the original sterol mixture contained from 30–35% of poriferasterol and 65–70% of clionasterol.

IV. *Haliclona viridis* (Duchaissaing and Michelotti) de Laubenfels. This common, soft, green sponge was collected in the shallow waters near Miami and Bermuda. The sponges from the different localities were investigated separately, but no significant differences in their composition were observed.

TABLE I

COMPOSITION OF DRIED *Haliclona* SPECIES

SPECIES	% OF TOTAL		% OF ORGANIC FAT	% OF FAT UNSAPON.	% OF UNSAPON. STEROL
	Spicules	Organic			
arbuscula	30	70	5	35	38
variabilis	8	92	7.2	24.5	63.5
coerulescens	7	93	2.6	48	67.5
permollis	20	80	13.5	30	44
viridis	25	75	5.8	30.5	68.5
rubens	20	80	3.7	76	14.5
longleyi	44	56	3.5	38.5	74

The acetate of the crude sterol obtained from this sponge melted at 120–130°; $[\alpha]_D^{25}$ −40°. Systematic fractionation of the more difficultly soluble bromides of the acetate mixture led to the isolation of a small amount of a tetrabromide of m.p. 200–205°. The high melting point of this product contradicts its identity with poriferasteryl acetate tetrabromide. Lack of material prevented further characterization of this product. The bulk of the material, the more difficultly soluble bromides, consisted of cholesteryl acetate dibromide, which was characterized by its conversion to cholesteryl acetate and cholesterol. Debromination of the more soluble bromides eventually lead to the isolation of an acetate of m.p. 136°; $[\alpha]_D^{27}$ −38°.

The sterol mixture of this sponge, therefore, consists of at least three components, of which cholesterol represents more than 50%. From 5–10% consists of a di-unsaturated sterol of the probable empirical formula, $C_{28}H_{46}O$. The remainder of the material shows similarity to clionasterol.

V. *Haliclona rubens* (Duchaissaing and Michelotti). This tall and thick red sponge was collected in the shallow waters of Biscayne Channel near Miami.

Its deep red pigment shows remarkable resistance against photo-oxidation, and it is only in part extracted by lipoid solvents. The acetate of the crude sterol obtained from this sponge melted at 130–135°; $[\alpha]_D^{25}$ −44°. Systematic fractionation gave results similar to those obtained with the sterol from the preceding sponge.

VI. *Haliclona longleyi* de Laubenfels. This ramose sponge was collected in Biscayne Bay, Miami, in 1945 and 1948. Investigated separately, the two lots gave practically identical results. The acetate of the sterol obtained from it melted at 140–141°; $[\alpha]_D^{27}$ −46.6°. Its unexpectedly high degree of uniformity was demonstrated by the fact that its properties did not change with numerous recrystallizations. Bromination of the acetate yielded a minute amount of a tetrabromide of m.p. 187–190°. The bulk of the material was a nicely crystalline dibromide of m.p. 125–126°. Addition of ethanol to a solution of the bromide in ether leads to the formation of a gelatinous precipitate which gradually changes into clear, thin prisms, up to one centimeter in length. This peculiar

TABLE II

PROPERTIES OF HALICLONASTEROL

DERIVATIVE	M.P., °C.	$[\alpha]_D^{\circ}$	$[M]_D^{\circ}$
sterol	140.5–141	−42	−168
steryl acetate	140–141	−46	−203
steryl acetate dibromide	125–126		
steryl benzoate	146.5	−15	−76
steryl *m*-dinitrobenzoate	209		
stanol	137.5	+18	+72
stanyl acetate	136.5	+11	+49
stanyl benzoate	133–134		
stanyl *m*-dinitrobenzoate	218		

behavior sets this dibromide apart from all other steryl acetate dibromides which have so far been described in the literature. Debromination of this product, and the various fractions obtained from the bromination mother liquors gave acetates with the same physical properties as the starting material.

The properties of the sterol obtained by way of the acetate, and those of a series of its derivatives are shown in Table II. They indicate the difference of this sterol from all other sterols which have so far been described. It is therefore proposed to name it *haliclonasterol*. The ready formation of an acetate dibromide, titration with perbenzoic acid, and quantitative catalytic hydrogenation prove the sterol to be mono-unsaturated. The differences between the molecular rotations of the sterol, its acetate and benzoate, and between those of the saturated and unsaturated derivatives (4) locate the double bond in 5,6-position. The results of the analyses of the steryl *m*-dinitrobenzoate, the stanyl *m*-dinitrobenzoate, and the acetate dibromide suggest the empirical formula $C_{28}H_{48}O$ for haliclonasterol. This sterol therefore appears to be an isomer of campesterol (5) and 22,23-dihydrobrassicasterol (6).

Unfortunately, lack of sufficient quantities of haliclonasterol has as yet prevented elucidation of the nature of this isomerism.

DISCUSSION

The investigations described above have shown that chalina (ostrea) sterol is not the typical sterol of all sponges which have at present been placed within the genus *Haliclona*. On the contrary, the presence of this sterol has been demonstrated in only one of the seven species which have so far been studied. There exists a lack of uniformity in the nature of the sterols which have been isolated from the other six sponges. The sterol mixtures of two of these contain one sterol in excess of 80% of the total, such as the poriferasterol of *H. variabilis*, and the new haliclonasterol of *H. longleyi*. The sterols of the other sponges are rather complex mixtures. A distinct similarity is noticeable in the composition of the mixtures obtained from *H. permollis* and *H. coerulescens*, and those from *H. viridis* and *H. rubens*. In the former the two major components appear to be poriferasterol and clionasterol. In the latter the most characteristic feature is the presence of substantial amounts of cholesterol which may exceed 50% of the total.

It is at present difficult to evaluate the significance of these observations. In future publications it will be shown that there exists a remarkable uniformity in the sterols isolated from various species of other sponge genera. The corresponding lack of uniformity among the species of *Haliclona* suggests that many species have been grouped within this genus which show only superficial relations to each other.

EXPERIMENTAL

All melting points are corrected. All optical rotations were taken in a 1-dm. tube, the sample being dissolved in 3.06 cc. of chloroform.

Preparation of the sterols. The air-dried sponges were ground and then thoroughly extracted with acetone in a large Soxhlet apparatus. After evaporation of the acetone, the residue was dissolved in benzene, and the water removed by co-distillation. In all instances certain amounts of smeary, brown, water-soluble material, remained undissolved in the benzene. The benzene extract was then evaporated to dryness, and the residue dried to constant weight at 80°. This acetone-benzene-soluble fraction is referred to as fat in Table I. The data in the table are all based on weights of crude sponge material from which the non-spicular ash has been subtracted as described in a previous communication (7). The saponification of the fat, and the isolation of the sterol was carried out as previously described. The sterol content of an aliquot part of the non-saponifiable fraction was determined by precipitation with digitonin. The crude sterol was at once acetylated by refluxing with acetic anhydride.

Haliclona variabilis. The crude acetate, (1.92 g.) m.p. 141–142°, after one recrystallization each from ether and chloroform-methanol gave poriferasteryl acetate (590 mg.), m.p. 147–148°; $[\alpha]_D^{27}$ −52° (36.5 mg.; α, −0.62°). Saponification yielded poriferasterol, m.p, 155.5–156°; $[\alpha]_D^{27}$ −50° (37.2 mg.; α, −0.61°). When mixed with authentic material these products did not show a depression of melting point.

A sample of acetate (840 mg.), obtained from the mother liquors was dissolved in ether (8 cc.) and treated with a 5% solution of bromine in glacial acetic acid (17 cc.). There was obtained a high-melting bromide (760 mg)., difficultly soluble in ether, which, after two

recrystallizations from ethyl acetate, afforded poriferasteryl acetate tetrabromide, m.p. 190–192°.

Anal. Calc'd for $C_{31}H_{50}Br_4O_2$: Br, 41.3. Found: Br, 42.0.

Debromination of the tetrabromide with zinc in glacial acetic acid gave poriferasteryl acetate, m.p. 146–147°; $[\alpha]_D$ −51°. Concentration of the bromination mother liquor gave further quantities of tetrabromide.

Haliclona permollis and H. coerulescens. The acetates of the sterols obtained from either sponge melted at 133–135°; $[\alpha]_D$ −40° to −44°. A sample of each of the acetates (350 mg.) was dissolved in ether (3 cc.) and treated with a 5% solution of bromine in glacial acetic acid (6 cc.). Both samples gave a tetrabromide difficulty soluble in ether, which after recrystallization from ethyl acetate melted at 189–192°.

Anal. Calc'd for $C_{31}H_{50}Br_4O_2$: Br, 41.3. Found: Br, 41.6.

Debromination of the tetrabromide with zinc in acetic acid gave poriferasteryl acetate, m.p. 146–147°; $[\alpha]_D^{27}$ −51°. Concentration of the bromination mother liquors gave a bromine-free acetate, which, after several recrystallizations from ethanol, melted at 135°.

Haliclona viridis. Recrystallization of the crude acetate gave two fractions: I, (650 mg.), m.p. 125–130°, and II, (780 mg.), m.p. 112–116°. Bromination of I (480 mg.), in ether (2.5 cc.) with 5% bromine-acetic acid solution (7.5 cc.) gave 465 mg. of precipitated bromides. Trituration of the bromide with ether gave an insoluble fraction (40 mg.) which after several recrystallizations from ether, by means of continuous extraction from a thimble, melted at 200–205°.

Anal. Calc'd for $C_{30}H_{48}Br_4O_2$: Br, 42.04. Found: Br, 41.86.

After several recrystallizations from ether-glacial acetic acid, the ether-soluble portion of the precipitated bromides afforded cholesteryl acetate dibromide, m.p. 115–116°.

Anal. Calc'd for $C_{29}H_{48}Br_2O_2$: Br, 27.16. Found: Br, 27.50.

Debromination with zinc in glacial acetic acid gave cholesteryl acetate, m.p. 114°; $[\alpha]_D^{27}$ −43°, and hydrolysis of the latter yielded cholesterol, m.p. 147°; $[\alpha]_D^{27}$ −38°. No depressions of melting point were observed when these derivatives were mixed with authentic material.

Fraction II (780 mg.) was brominated as before, and the precipitated bromide separated into an ether-soluble and an insoluble fraction. The former yielded cholesteryl acetate dibromide (360 mg.).

The mother liquors from the brominations of fractions I and II were debrominated with zinc. The acetate thus obtained was rebrominated, and the soluble fraction debrominated as before. The acetate thus obtained, after numerous recrystallizations from ethanol, melted at 137°; $[\alpha]_D^{27}$ −42°. It gave no depression of melting point when mixed with clionasteryl acetate.

Haliclona rubens. The unsaponifiable fraction of this sponge was not a wax-like solid like that of most other sponges, but an oil of a rather low viscosity. The presence of the oil and of an amorphous, white substance made difficult the usual extraction of the sterol with hot methanol. Many recrystallizations from methanol and several treatments with Norit were required before a colorless sterol was obtained.

The crude acetate (1.12 g.), m.p. 130–135°; $[\alpha]_D^{27}$ −43°, was brominated as before, and the precipitated fraction (485 mg.), separated on the basis of solubility in ether. After two crystallizations from ethyl acetate, the insoluble fraction (120 mg.) melted at 195–200°.

Anal. Calc'd for $C_{30}H_{48}Br_4O_2$: Br, 42.0. Found: Br, 41.9.

The soluble fraction yielded cholesteryl acetate dibromide, m.p. 114–115°. The bromination mother liquors were debrominated with zinc, and the acetate thus obtained saponified. Bromination of the resulting sterol (320 mg.) in ether and glacial acetic acid gave cholesterol dibromide (90 mg.), m.p. 112–114°. Debromination of the soluble bromides, and acetylation of the resulting product gave an acetate, which after several recrystallizations from ethanol, melted at 135–136°; $[\alpha]_D^{27}$ −42°.

Haliclona longleyi. Haliclonasteryl acetate. The crude acetate melted at 139–140°. After

several recrystallizations from anhydrous ether in a Skau-tube, the melting point remained constant at 140–141°; $[\alpha]_D^{27}$ −46.5° (23.0 mg.; α, −0.35°). The acetate, purified over the dibromide, melted at 140°; $[\alpha]_D^{27}$ −46° (43.9 mg.; α, −0.66°).

Anal. Calc'd for $C_{30}H_{50}O_2$: C, 81.4; H, 11.4.

Found: C, 81.1; H, 11.3.

Haliclonasteryl acetate dibromide. A sample of the acetate (700 mg.) was dissolved in ether (7 cc.) and treated with a 2.5% solution of bromine in glacial acetic acid (20 cc.). After 24 hours there had formed 90 mg. of a precipitate of which 30 mg. was difficultly soluble in ether. After one recrystallization from ethyl acetate this tetrabromide melted at 187–190°.

Anal. Calc'd for $C_{30}H_{48}Br_4O_2$: Br, 42.0. $C_{31}H_{50}Br_4O_2$: Br, 41.3.

Found: Br, 42.2.

The ether-soluble fraction of the first precipitate was combined with the bromination mother liquor, and the mixture left standing in an open vessel at room temperature to permit gradual evaporation of the ether. After several days long, clear prisms began to separate. They were washed with glacial acetic acid and methanol, and dried *in vacuo;* (425 mg.), m.p. 125°. After recrystallization from ether-glacial acetic acid and ethyl acetate, the bromide melted at 125–126°. Fractions recovered from various mother liquors showed the same melting point. The peculiar behavior of the bromide upon recrystallization from ether-ethanol has been discussed in the introduction.

Anal. Calc'd for $C_{30}H_{50}Br_2O_2$: C, 59.80; H, 8.36; Br, 26.53.

$C_{31}H_{52}Br_2O_2$: C, 60.39; H, 8.50; Br, 25.92.

Found: C, 59.75; H, 8.43; Br, 26.52.

Debromination of various fractions of bromide and of the final bromination mother liquor gave haliclonasteryl acetate of m.p. 139–141°; $[\alpha]_D^{27}$ −46° to −47°.

Haliclonasterol. The sterol was obtained by saponification of the acetate. The crude product melted at 140–141°, and after two recrystallizations from ether, sharply at 140.5–141°; $[\alpha]_D^{27}$ −41.5° (40.6 mg.; α, −0.55°). The sterol contained solvent of crystallization which could not be completely removed.

Haliclonasteryl benzoate. A sample of sterol (50 mg.) was dissolved in pyridine (1 cc.) and benzoyl chloride (0.2 cc.) was added to the solution. After 48 hours methanol was added to the solution until a copious precipitate had been obtained. This was washed thoroughly with methanol and recrystallized several times from acetone, m.p. 146.5°; $[\alpha]_D^{27}$ −14.7° (33.3 mg.; α, −0.16°).

Anal. Calc'd for $C_{35}H_{52}O_2$: C, 83.3; H, 10.4.

Found: C, 83.1; H, 10.5.

Haliclonasteryl m-dinitrobenzoate. This derivative was prepared in a manner analogous to the one described above. The dinitrobenzoate was recrystallized from benzene-methanol and ethyl acetate, m.p. 209°.

Anal. Calc'd for $C_{35}H_{50}N_2O_6$: C, 70.67; H, 8.47.

$C_{36}H_{52}N_2O_6$: C, 71.02; H, 8.61.

Found: C, 70.7; H, 8.4.

Haliclonastanyl acetate. Haliclonasteryl acetate was hydrogenated in ethyl acetate at room temperature and atmospheric pressure with a platinum black catalyst (Willstätter). The hydrogenated material gave a negative Liebermann-Burchard reaction. It was recrystallized several times from ether in a Skau-tube, m.p. 136–136.5°; $[\alpha]_D^{27}$ +10.6° (23.0 mg.; α, +0.08°).

Anal. Calc'd for $C_{30}H_{52}O_2$: C, 81.02; H, 11.79.

Found: C, 81.06; H, 12.31.

Haliclonastanol. It was obtained by saponification of the acetate. After recrystallization from chloroform-methanol and ether, the stanol was obtained in the form of small needles of m.p. 137–137.5°; $[\alpha]_D^{27}$ +18.2 (30.6 mg.; α, +0.18°). The stanol contains solvent of crystallization which could not be removed completely.

Haliclonastanyl m-dinitrobenzoate. This derivative was prepared as described above. After several recrystallizations from benzene-ethanol and ethyl acetate it melted at 217.5–218°.

Anal. Calc'd for $C_{35}H_{52}N_2O_6$; C, 70.44; H, 8.78.
$C_{36}H_{54}N_2O_6$; C, 70.78; H, 8.91.
Found: C, 70.37; H, 8.85.

Haliclonastanyl benzoate. This derivative was prepared in the usual manner. It shows a peculiar behavior upon recrystallization from chloroform-methanol. There is first formed a light flocculent material which gradually changes into small needles, which upon heating turn turbid at 130° and clear at 133°. The same phenomenon is observed when the benzoate is recrystallized from ether. After several such crystallizations, the benzoate melted to a clear liquid at 133.5°, the first turbidity appearing at 131°.

SUMMARY

1. The sterols of six species of sponges of the genus *Haliclona* have been isolated and investigated.

2. Poriferasterol has been shown to be the principal sterol of *Haliclona variabil s.*

3. The sterols from *H. permollis* and *H. coerulescens* have been shown to be mixtures containing poriferasterol and probably clionasterol.

4. The sterols from *H. viridis* and *H. rubens* have been shown to be mixtures containing more than 50% cholesterol.

5. *Haliclona longleyi* has been shown to contain a new sterol in a remarkably high degree of purity. The name of haliclonasterol has been proposed for this compound which is mono-unsaturated and of the probable formula $C_{28}H_{48}O$. A number of derivatives of haliclonasterol have been described.

6. The possible significance of these observations has been discussed.

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[Contribution from the Sterling Chemistry Laboratory and the Bingham Oceanographic Laboratory, Yale University]

CONTRIBUTIONS TO THE STUDY OF MARINE PRODUCTS. XXIV THE OCCURRENCE OF BRASSICASTEROL IN MOLLUSKS

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In the Vth communication of this series (1) the statement was made that the sterol mixture obtained from the oyster, *Ostrea virginica*, contains small amounts of stigmasterol. The identification of this sterol was based primarily on the properties of the steryl acetate tetrabromide. It has been suggested, however, in a later communication (2) that the sterol in question was brassicasterol rather than stigmasterol, and that shakosterol, first isolated by Tsujimoto (3) from *Tridacne gigas*, is also identical with brassicasterol. Lack of adequate amounts of starting material has so far delayed the isolation of pure brassicasterol from the oyster. No difficulties, however, were encountered in isolating substantial quantities of this sterol from another bivalve, the mussel, *Modiolus demissus*. The starting material was a mussel sterol mixture, a large amount of which had been obtained through the courtesy of the Silmo Laboratories. This mixture contained only insignificant quantities of 7-dehydrosterols, the bulk of them having first been removed by fractional crystallization. The isolation of brassicasterol was carried out by way of the difficultly-soluble acetate tetrabromide, obtained by fractionation of the acetate bromide mixture. Fractionation of the lower-melting, difficultly-soluble, acetate bromides eventually led to the isolation of cholesteryl acetate dibromide.

While these investigations were nearing completion, the authors received a series of reprints of papers by Toyama and collaborators which had been published in Japan during the war years. In the VIIth communication of their series (4a), the Japanese authors have indicated the presence of brassicasterol in the sterol mixture obtained from the bivalve, *Corbicula leana*, and in a subsequent paper (4b), they have convincingly demonstrated its occurrence in the oyster, *Ostrea gigas*. In addition the dissertation of van der Vliet (5) contains a reference to some unpublished work by Stevens, according to which the presence in the mussel, *Mytilus edulis*, of brassicasterol and cholesterol has been ascertained. The occurrence of brassicasterol in bivalves has therefore been demonstrated by three independent groups, and the identity of shakosterol and brassicasterol has been made more probable if not certain.

The more recent Japanese literature contains the description of several other new sterols from bivalves. The physical properties of these sterols and their known derivatives are shown in Table I. The most unique and interesting sterol of this group is corbisterol, which Matsumoto and Toyama (4c) have isolated from the sterol mixture of *Corbicula leana*. On the basis of iodine numbers and saponification values, the Japanese authors have concluded that corbisterol is a tetra-unsaturated sterol of the empirical formula $C_{29}H_{44}O$ or $C_{28}H_{42}O$. An evaluation of the differences between the molecular rotations of the sterol and its acetate, and of corresponding saturated and unsaturated derivatives [Barton (6)],

however, strongly indicates that corbisterol is a $\Delta^{5,7}$-di-unsaturated sterol. Such a suggestion is supported, rather than contradicted by the high iodine number reported by the Japanese authors, for it is well known that 7-dehydrosterols are prone to give iodine numbers substantially higher than the theoretical values.

It is well established that the sterol mixtures of certain mollusks contain such substantial quantities of 7-dehydrosterols, as to have made them a commercial source for provitamin-D. The isolation of 7-dehydrosterol from a gastropod has been claimed in a patent by Boer, *et al.* (7), and Kind and Herman (8) have recently intimated its identity with 7-dehydroclionasterol (9). Van der Vliet (5, 10) has concluded on the basis of indirect evidence, derived from a systematic study of irradiation products, that the "mussel provitamin-D" of *Mytilus edulis*, consists of ergosterol, 7-dehydrocholesterol, $\Delta^{5,7,22}$-cholestatrien-3-ol, and an unknown sterol. It appears quite unlikely that corbisterol is identical with any one of the named 7-dehydrosterols. The probability, however, is indicated that it is essentially 22,23-dihydroergosterol, or more likely a mixture of this sterol with its 24-methyl epimer, the as yet unknown 7-dehydrocampesterol.

TABLE I

NEW MOLLUSK STEROLS

STEROL	STEROL		ACETATE		BENZOATE		STANOL		STANYL ACETATE	
	M.p., °C	$[\alpha]_D$°	M.p., °C	$[\alpha]_D$°	M.p., °C	$[\alpha]_D$°	M.p., °C	$[\alpha]_D$°	M.p., °C	$[\alpha]_D$°
Corbisterol (4c)	149	−93.5	151	−70.4	141–144	−45	142.5	+26	140	+13
Conchasterol (12)	133–134		144–145							
Meretristerol (11)	134.5	−44	144–145	−50.2	141–145	−20	146.5		140	+13
Pectosterol (13) ..	134–137	−35	137							
Magakisterol (14) .	152.8	−47	149.5	−52						

Toyama and Yajima believe that the meretristerol of the bivalve, *Meretrix meretrix* (11), is identical with Tsujimoto's conchasterol (12). They nevertheless prefer continuing the use of the new name until the question of the identity of the two sterols has been definitely demonstrated. Tsujimoto had originally regarded conchasterol as an isomer of cholesterol. Toyama and Yajima have concluded, however, on the basis of iodine numbers and saponification values, that meretristerol and hence conchasterol are di-unsaturated compounds of the probable formula $C_{28}H_{46}O$. An analysis of the differences between the molecular rotations of the sterol, its acetate and benzoate, and of the steryl and stanyl acetate supports this view, and in addition indicates the locations of the double bonds in the $\Delta^{5,22}$-positions. It remains as yet uncertain, however, that this sterol is a new isomer of brassicasterol and chalinasterol (ostreasterol) (2). The probability is strongly indicated that meretristerol and conchasterol represent some of the difficultly separable mixtures of these two 24-methyl epimers which are frequently encountered among the sterols of bivalves (2). Both these sterols afford rather insoluble acetate tetrabromides. The failure of the Japanese authors to obtain such bromides from meretristeryl acetate is probably due to

the fact that the bromination, as described by them, was carried out in a solution too dilute to permit ready separation of the adduct. The data furnished in support of the claims that pectosterol (13) and magakisterol (14) are new compounds are far too inadequate to warrant any comments concerning their probable structure.

EXPERIMENTAL

All melting points are corrected. All optical rotations were taken in a 1 dm. tube, the sample being dissolved in 3.06 cc. of chloroform.

Brassicasteryl acetate tetrabromide. The crude sterol mixture was acetylated by refluxing with acetic anhydride in the usual manner, and the acetate recrystallized once from a mixture of chloroform and methanol. To a solution of 220 g. of the crude acetate in 1200 cc. of ether was added, with stirring and cooling, 1100 cc. of a 10% solution of bromine in glacial acetic acid. The mixture was kept in a refrigerator overnight. The crystalline bromides were washed with acetic acid and methanol, and dried *in vacuo* over sodium hydroxide. The total, 176.5 g., was then digested with 1 liter of ether at room temperature. The undissolved material was collected, washed with small amounts of ether and dried. The tetrabromide thus obtained weighed 41 g.; upon heating it decomposed above 180°. For further purification it was extracted from a thimble with boiling ether; yield 39 g., m.p. (dec.) 205–209°. Subsequent recrystallization of the tetrabromide from chloroform-methanol raised the decomposition point to 209–216°.

Anal. Calc'd for $C_{30}H_{48}Br_4O_2$: Br, 42.0. Found: Br, 41.8.

Brassicasteryl acetate. Debromination of the tetrabromide with zinc dust and glacial acetic in the usual manner afforded a product which after two recrystallizations from a mixture of acetone and methanol gave brassicasteryl acetate, m.p. 152°; $[\alpha]_D^{25}$ −62.2° (52.7 mg., α, −1.07°).

Brassicasteryl acetate 22,23-dibromide. The partial debromination of the tetrabromide with sodium iodide in ethanol was carried out according to the directions of Fernholz and Stavely (15). The 22,23-dibromide thus obtained was recrystallized several times from a mixture of ether and methanol; m.p. 213–217°.

Anal. Calc'd for $C_{30}H_{48}Br_2O_2$: Br, 26.7. Found: Br, 27.0.

The melting point reported for brassicasteryl acetate 22,23-dibromide is 236–238° (15). In this laboratory, however, various samples of the dibromide have been found to melt with decomposition between 210 and 220°. Debromination of the above dibromide with zinc in glacial acetic acid afforded brassicasteryl acetate of m.p. 152°.

Brassicasteryl benzoate. This derivative was prepared in the usual manner by treating the sterol with benzoyl chloride in pyridine. It was recrystallized several times from ether; m.p. 163°; $[\alpha]_D^{25}$ −35° (30.0 mg., α, −0.34°).

Cholesteryl acetate. The ether extract of the original acetate bromide mixture was concentrated under a stream of nitrogen until the appearance of crystalline material. This was removed, and the concentration process was repeated. After the removal of a second crop of crystals, methanol was added to the mother liquor. until a copious precipitate of cholesteryl acetate dibromide was obtained. The dibromide was recrystallized from a mixture of ether and methanol, m.p. 111°. Debromination of the dibromide with zinc in glacial acetic acid gave cholesteryl acetate, m.p. 113–114°; $[\alpha]_D^{25}$ −45° (71.1 mg., α −1.03°). Hydrolysis of the acetate gave cholesterol, m.p. 147°; $[\alpha]_D^{25}$ −39.5° (75.2 mg., α, −0.97°).

SUMMARY

It has been demonstrated that the sterol mixture obtained from the mussel, *Modiolus demissus*, contains significant quantities of brassicasterol and cholesterol.

The suggestion has been made that corbisterol is a 7-dehydrosterol, and that it is probably identical with 22,23-dihydroergosterol.

It has also been suggested that meretristerol and conchasterol are mixtures of brassicasterol and chalinasterol.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MISSOURI]

THE HYDROGENATION OF AROMATIC KETONES WITH HYDROGEN AND COPPER-CHROMIUM OXIDE CATALYST

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A number of aromatic ketones have been reduced to the corresponding carbinols and alkylbenzenes in good yields by means of hydrogen and copper-chromium oxide catalyst. When the ketones were hydrogenated at temperatures of 100–130°, the product was the secondary carbinol. This carbinol was in turn hydrogenated at 180–195° without solvent or at 200–250° with solvent to the aromatic hydrocarbon. The data for these reductions are summarized in Tables I, II, and III.

The presence of one, two, or three methyl groups on the benzene nucleus and the branching of the alkyl group had little effect on the temperature at which the carbonyl group was reduced to carbinol. *n*-Butyrophenone, *p*-methyl-*n*-butyrophenone, and the three dimethyl-*n*-butyrophenones were reduced to carbinols at 110–130° during two hours. With two methyl groups *ortho* to the carbonyl group in the two mesitylene ketones only a slight increase in temperature was necessary. The relatively small variations in reduction temperature may perhaps be due to variations in pressure or to catalyst poisons rather than to a hindering effect of the methyl groups.

As a matter of interest, the reduction study was extended to include representative phenolic aldehydes and ketones and methoxyaldehydes listed in Table III. The *o*- and *p*-methoxybenzaldehydes were reduced to the corresponding methoxybenzyl alcohols at 110–125°, the same temperature range required for the reduction of aromatic ketones to alcohols, and *p*-methoxybenzyl alcohol yielded *p*-cresol methyl ether at 185° in methanol solution.

When the hydroxyl group was not methylated and was *ortho* or *para* to the aldehyde group, *o*- and *p*-cresol were obtained at 110–130°, while *m*-hydroxybenzaldehyde required a temperature of 185° to form *m*-cresol. At 250°, *o*-hydroxybenzaldehyde yielded a small amount of 2-methylcyclohexanol. To minimize possible polymerization of the intermediate hydroxybenzyl alcohols, methanol was used as solvent for the reduction of the phenolic aldehydes.

The *o*- and *p*-hydroxyacetophenones and the *o*- and *p*-hydroxypropiophenones were also reduced to alkylphenols at 110–130°. This reaction should furnish a convenient method for the preparation of alkylphenols.

From these data it appears that when a phenolic group is *ortho* or *para* to the carbonyl group of an aromatic aldehyde or ketone, the carbinol group is

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reduced to the methylene group at the temperature (110–130°) at which the non-phenolic aldehydes and ketones are reduced to carbinols. A phenolic group *meta* to the carbonyl group appears to have no effect on the course of the reduction of the phenolic aldehyde, and a temperature of 185° was required to convert the carbonyl to methylene.

The results from the hydrogenation of ten of the aromatic ketones with Raney nickel as catalyst indicate that it is of limited usefulness in the preparation of aromatic hydrocarbons. Ketones such as acetophenone and propiophenone could be hydrogenated at 65–85° and 200 atm. to yield a product containing up to 75% of aromatic hydrocarbon and variable amounts of aromatic carbinol and naphthene carbinol. Higher temperatures increased the proportion of naphthene carbinol. Some of the ketones derived from *m*-xylene such as 2,4-

TABLE I

HYDROGENATION OF AROMATIC KETONES TO CARBINOLS

COMPOUND	TEMP., °C.	TIME, HRS.	YIELD, WT., %	PRODUCTS
Acetophenone[a]	100–120	0.1	63	Methylphenyl carbinol
			5	Ethylbenzene
n-Butyrophenone[b]	120–130	2.0	74	*n*-Propylphenylcarbinol
			18	*n*-Butylbenzene
4-Methyl-*n*-butyrophenone[b]	110–125	2.0	89	(4-Methylphenyl)propylcarbinol
			6	1-Methyl-4-*n*-butylbenzene
2,4-Dimethyl-*n*-butyrophenone[a]	110–130	2.2	90	(2,4-Dimethylphenyl)-*n*--propylcarbinol
			2	1,3-Dimethyl-4-*n*-butylbenzene
2,4-Dimethyl-*n*-caprophenone[b]	175	2.2	92	(2,4-Dimethylphenyl)-*n*-amylcarbinol
			5	1,3-Dimethyl-*n*-hexylbenzene
Acetomesitylene[a]	110–130	1.5	96	(2,4,6-Trimethylphenyl)methylcarbinol
Propiomesitylene[a]	135	1.5	87	(2,4,6-Trimethylphenyl)ethylcarbinol

[a] The ketone (0.25 mole) in 100 ml. of anhydrous methanol was reduced with hydrogen at 220–240 atm. using 4.0 g. of copper-chromium oxide catalyst.

[b] No solvent.

dimethyl-*n*-butyrophenone and 2,4-dimethylisobutyrophenone required a temperature of 175–195° at 240 atm. for reduction to the aromatic hydrocarbon in 80% yield, while 2,4-dimethyl-*n*-caprophenone reduced with a different preparation of catalyst at 160° to yield a mixture of naphthene hydrocarbon and aromatic hydrocarbon. Adkins (1) reports that acetomesitylene is stable toward Raney nickel at 150° but at 160° we have obtained a 22% yield of ethylmesitylene along with methyl (2,4,6-trimethylphenyl)carbinol. Propiomesitylene reduced similarly.

The addition of small amounts of aqueous sodium hydroxide or sodium 2,6-di-*n*-propylphenol did not facilitate the reduction of these ketones as it did with phenolic ketones (2).

Apparently the activity of the catalyst and to some extent the number of alkyl groups present on the aromatic nucleus affect the course of the reduction when Raney nickel is used as the catalyst.

TABLE II

HYDROGENATION OF AROMATIC KETONES AND CARBINOLS TO HYDROCARBONS[a]

COMPOUND	TEMP., °C.	TIME, HRS.	YIELD, WT. %	PRODUCTS
Acetophenone	235		83	Ethylbenzene
n-Butyrophenone	240		74	*n*-Butylbenzene
4-Methylacetophenone	250–270	0.5	91	*p*-Ethyltoluene
4-Methylpropiophenone	250–270	1.25	83	*p*-*n*-Butyltoluene
2,4-Dimethylacetophenone	250	0.5	84	1,3-Dimethyl-4-ethylbenzene
2,4-Dimethylpropiophenone	250	0.5	74	1,3-Dimethyl-4-*n*-propylbenzene
2,4-Dimethyl-*n*-butyrophenone	250	1.5	86	1,3-Dimethyl-4-*n*-butylbenzene
2,4-Dimethylisobutyrophenone	250–260	0.5	83	1,3-Dimethyl-4-isobutylbenzene
2,4-Dimethylisovalerophenone	250–260	0.5	89	1,3-Dimethyl-4-isoamylbenzene
2,4-Dimethyl-*n*-caprophenone	250	0.5	91	1,3-Dimethyl-*n*-hexylbenzene
2,4-Dimethylisocaprophenone	250	0.5	87	1,3-Dimethyl-4-isohexylbenzene
3,4-Dimethyl-*n*-butyrophenone	250	0.5	77	1,2-Dimethyl-4-*n*-butylbenzene
2,5-Dimethyl-*n*-butyrophenone	250	0.5	86	1,4-Dimethyl-2-*n*-butylbenzene
Propiomesitylene	250	0.5	82	*n*-Propylmesitylene
Phenylmethylcarbinol	250	0.75	89	Ethylbenzene
Phenyl-*n*-propylcarbinol	180–195	2.0	88	*n*-Butylbenzene
(4-Phenylmethyl)-*n*-propylcarbinol)	180–190	2.0	93	1-Methyl-4-*n*-butylbenzene
(2,4-Dimethylphenyl)-*n*-propylcarbinol)	180–195	2.1	95	1,3-Dimethyl-4-*n*-butylbenzene
(2,4-Dimethylphenyl)-*n*-amylcarbinol)	180–195	2.0	95	1,3-Dimethyl-4-*n*-hexylbenzene
(2,4,6-Trimethylphenyl)methylcarbinol	180–195	1.75	43	1,3,5-Trimethyl-2-ethylbenzene
			44	Unchanged carbinol

[a] The ketones (0.25 mole) in 100 ml. of anhydrous methanol were reduced with hydrogen at 300 to 340 atm. using 4.0 g. of copper-chromium oxide catalyst. The carbinols (0.25 mole) were reduced in the absence of solvent with hydrogen at 270 atm using 4.0 g. of copper-chromium oxide catalyst.

TABLE III

HYDROGENATION OF METHOXY- AND PHENOLIC ALDEHYDES AND KETONES[a]

COMPOUND	TEMP., °C.	TIME, HRS.,	YIELD, WT., %	PRODUCTS
o-Hydroxybenzaldehyde	123–135	2.3	86	*o*-Cresol
p-Hydroxybenzaldehyde	110–125	1.5	73	*p*-Cresol
			8	*p*-Hydroxybenzyl alcohol
m-Hydroxybenzaldehyde	110–125	2.0	4	*m*-Cresol
			84	*m*-Hydroxybenzyl alcohol
o-Methoxybenzaldehyde	110–125	2.0	88	*o*-Methoxybenzyl alcohol
p-Methoxybenzaldehyde	130		83	*p*-Methoxybenzyl alcohol
p-Methoxybenzyl alcohol	185	2.5	85	*p*-Methylanisole
o-Hydroxyacetophenone	115–130	2.2	91	*p*-Ethylphenol
o-Hydroxypropiophenone	115–125	0.25	89	*o*-Propylphenol
p-Hydroxyacetophenone	140	0.5	75	*p*-Ethylphenol
p-Hydroxypropiophenone	115–125	3.5	79	*p*-*n*-Propylphenol

[a] The compound (0.25 mole) in 100 ml. of methanol was reduced with hydrogen at 220 to 240 atm. using 4.0 g. of copper-chromium oxide catalyst.

Five ketones derived from toluene and *m*-xylene were reduced by the modified Wolff-Kishner method (3). Of the chemical methods for reducing aromatic ketones to hydrocarbons, this method has been the most satisfactory. Yields were good, and the aromatic hydrocarbon was free of olefins and carbinols which are by-products of the Clemmensen reduction.

TABLE IV

PHYSICAL CONSTANTS OF COMPOUNDS NOT DESCRIBED IN THE LITERATURE

	B.P., °C.	MM.	n_D^{20}	FORMULA	CALC'D C	CALC'D H	FOUND C	FOUND H
2,4-Dimethyl-*n*-caprophenone	133	5	1.5170	$C_{14}H_{20}O$	82.30	9.87	82.08	9.89
2,4-Dimethylisocaprophenone	120	5	1.5123	$C_{14}H_{20}O$	82.30	9.87	82.25	9.76
Ethylcyclohexylcarbinol	96	18	1.4688	$C_9H_{18}O$	75.99	12.76	75.93	12.8
n-Propylcyclohexylcarbinol	115	40	1.4652	$C_{10}H_{20}O$	76.84	12.91	77.02	12.66
(4-Methylphenyl)-*n*-propylcarbinol	98	4	1.5137	$C_{11}H_{16}O$	80.44	9.82	80.31	9.96
(2,4-Dimethylphenyl)-*n*-propylcarbinol	142	19	1.5151	$C_{12}H_{18}O$	80.90	10.11	80.73	10.37
(2,4-Dimethylphenyl)isopropylcarbinol	138	18	1.5155	$C_{12}H_{18}O$	80.90	10.11	80.98	10.41
(2,4-Dimethylphenyl)isobutylcarbinol	145	25	1.5120	$C_{13}H_{20}O$	81.25	10.41	81.10	10.61
(2,4-Dimethylphenyl)-*n*-amylcarbinol	122	2	1.5125	$C_{14}H_{22}O$	81.50	10.75	81.38	10.98
(3,4-Dimethylphenyl)-*n*-propylcarbinol	139	11	1.5183	$C_{12}H_{18}O$	80.84	10.18	80.87	10.26
(2,4,6-Trimethylphenyl)methylcarbinol[a]	93	2		$C_{11}H_{16}O$	80.44	9.82	80.35	9.86
(2,4,6-Trimethylphenyl)ethylcarbinol	112	5	1.5271	$C_{12}H_{18}O$	80.84	10.18	80.74	10.37
1,3-Dimethyl-4-*n*-hexylbenzene	102	2	1.4962	$C_{14}H_{22}$	88.35	11.65	88.50	11.65
1,3-Dimethyl-4-isohexylbenzene	96	2	1.4928	$C_{14}H_{22}$	88.35	11.65	88.32	11.76
1,2-Dimethyl-4-*n*-butylbenzene	93	8	1.4989	$C_{12}H_{18}$	88.82	11.18	88.76	11.12
1,4-Dimethyl-2-*n*-butylbenzene	85	6	1.4996	$C_{12}H_{18}$	88.82	11.18	88.84	11.16
1-(2,4-Dimethylphenyl)-1-butene	110	20	1.3340	$C_{12}H_{16}$	90.00	10.00	89.94	10.12

[a] M.p. 72–72.5°

EXPERIMENTAL[3]

All of the carbonyl compounds were refluxed over Raney nickel and distilled from the nickel as the final step in their purification.

Several of the carbinols were prepared for reference purposes by the reduction of the ketones with aluminum isopropoxide (4). When 2,4-dimethyl-*n*-butyrophenone was reduced with aluminum isopropoxide, the product was the olefin, 1-(2,4-dimethylphenyl)-1-butene.

The copper chromium oxide catalyst was prepared by the usual method (5). The Raney nickel catalyst was prepared by the method of Mozingo (6).

Hydrogenations. (a) *With copper-chromium oxide.* The hydrogenations were carried out in a rocking steel autoclave.[4] Normally, 0.25 mole of ketone, aldehyde, or alcohol and 4 g.

[3] The semimicro carbon-hydrogen analyses are by Richard A. Carpenter and Karl T. Zilch.

of copper chromium oxide were placed in a copper liner having a total capacity of 500 ml. When a solvent was used, 100 ml. of anhydrous analytical reagent methanol was added. Yields were nearly identical with or without methanol except in the case of the phenolic aldehydes, which formed variable amounts of resinous products when they were reduced without solvent.

The temperature at which hydrogen was first absorbed was noted by plotting pressure against temperature. When the carbinol was the desired product, the temperature was held at this point until the pressure became constant. If the hydrocarbon was to be the final product and methanol was the solvent, the temperature was raised to 200–250° and held there until reduction was complete. Without solvent, the carbinol was usually reduced to hydrocarbon at 180–195°. The reaction time listed in the tables represents the interval of time from the start of the reaction at room temperature until the pressure became constant.

The contents of the liner were washed out with methanol if it had been used as solvent, or with benzene if no solvent had been used, and filtered. When the reduction products (notably the monoalkylbenzenes) formed azeotropic mixtures with methanol, the reaction mixture was diluted with an equal volume of water, the oily layer was separated, and the aqueous layer was extracted three times with small portions of benzene. The benzene extracts were combined with the oily layer, the solution was dried and fractionated through a micro column of approximately fifteen theoretical plates with a reflux ratio of 5:1 to 10:1 depending on the closeness of the boiling points of the compounds to be separated.

(b) *Reductions with Raney nickel.* The reductions were carried out and the products isolated as described above. Usually 0.25 mole of ketone, 3 g. of Raney nickel, and 60 cc. of anhydrous methanol were placed in the copper liner. The initial hydrogen pressure was approximately 200 atm. at room temperature.

The known hydrocarbons, carbinols, and alkylphenols were identified by their physical constants or by their derivatives. The physical constants and analyses of compounds not previously described in the literature are listed in Table IV.

SUMMARY

Aromatic ketones and methoxy aromatic aldehydes may be hydrogenated over copper-chromium oxide catalyst at an initial hydrogen pressure of 220–340 atm. to form the corresponding carbinol at 110–130° or the alkylbenzene or cresol at 184–250°. Yields are nearly quantitative.

The *o*- and *p*-hydroxybenzaldehydes were reduced to *o*- and *p*-cresol at 110–130° while *m*-hydroxybenzaldehyde required a temperature of 185° to form *m*-cresol.

The *o*- and *p*-hydroxy ketones were reduced to alkylphenols at 110–130°.

Raney nickel is of limited usefulness as a catalyst for the reduction of aromatic ketones to alkylbenzenes.

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[Contribution from the Eastern Regional Research Laboratory[1]]

PREPARATION AND PROPERTIES OF MONOMERIC AND POLYMERIC ACRYLIC ESTERS OF ETHER-ALCOHOLS[2]

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An earlier paper (1) from this Laboratory reported the acrylic esters of the methyl, ethyl, and butyl monoethers of glycol. They had been made by the pyrolysis of the corresponding α-acetoxypropionates. Only low yields were obtained, and no description of their polymers was given. The present work was intended to develop a more satisfactory method of preparing these and similar esters and to determine some of the properties of their polymers.

Since many acrylic esters had been previously prepared in this Laboratory by the alcoholysis of methyl or ethyl acrylate (2–6), this method was used in the present work. In most cases this method was satisfactory, and the yields were high.

The monomeric esters were colorless, mobile liquids having characteristic mild odors. Table I shows the yields, physical constants and analytical data.

Polymeric esters. In general, the acrylates and methacrylates of ether-alcohols appeared to polymerize much more readily than did the alkyl esters (3–5).

Most of the esters were polymerized in bulk, in emulsion and in solution. The polymers were usually soft, elastic and rubbery, and most of those prepared in solution were tacky. The brittle points of the polymers of several of the alkoxyethyl acrylates were determined and may be compared with those of alkyl acrylates of approximately equal molecular weight: methoxyethyl, −25° (*n*-butyl, −45°); ethoxyethyl, −40° (*n*-amyl, −53°); butoxyethyl, −54° (*n*-heptyl, −59°); and isopropoxyethyl, −28°. These data show that the polymers of the first several *n*-alkoxyethyl acrylates have higher brittle points than the corresponding *n*-alkyl polyacrylates but the difference diminishes as the molecular weight of the monomer increases.

The polymers prepared in solutions of less than about 40% concentration were completely soluble, whereas those prepared in bulk or emulsion usually contained some insoluble, gelled material.

Air-curing of polymers. Exposure of the soluble polymers to air at room temperature for several weeks or at 100–150° for a few hours resulted in the formation of hard, tough, glossy, non-tacky, insoluble and infusible surface films.

Addition of benzoyl peroxide (5%) or soluble cobalt salts, such as the naphthenate or 2-ethylhexoate (0.01–.05%), greatly accelerated the cure, so that some cured in only 8 to 10 minutes at 100°. Large masses or thick films of the polymers cured only on their exposed surfaces, regardless of catalyst, time or

[1] One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture.

[2] Presented in part before the Division of Paint, Varnish, and Plastics Chemistry of the American Chemical Society, Atlantic City, N. J., April, 1946.

[3] Present address: Corn Products Refining Company, Argo, Illinois.

TABLE I

ACRYLIC ESTERS OF ETHER-ALCOHOLS

ACRYLATE	B.P., °C	MM.	YIELD, %	n_D^{20}	d_4^{20}	MOL. REFRACTION		SAPON. EQ.		ANALYSES C		ANALYSES H	
						Calc'd	Found	Calc'd	Found	Calc'd	Found	Calc'd	Found
2-Methoxyethyl[a]	59	12	96	1.4272	1.0131	32.74	33.00	130.1	128.3	55.4	55.2	7.7	7.8
2-Ethoxyethyl[a]	78	23	96	1.4282	0.9819	37.36	37.79	144.2	144.4	58.3	58.3	8.4	8.4
2-(2-Chloroethoxy)ethyl	74	0.8	63	1.4580	1.1471	42.22	42.49	89.3	91.7	47.1	47.4	6.2	6.6
2-Isopropoxyethyl[a]	82	19	95	1.4258	0.9549	41.97	42.44	158.2	158.6	60.7	60.8	8.9	9.2
2-Butoxyethyl[a]	64	2	95	1.4323	0.9497	46.59	47.07	172.2	173.3	62.8	62.7	9.4	9.3
2-(2-Ethylhexoxy)ethyl	87	0.5	90	1.4408	0.9215	65.06	65.40	228.3	226.2	68.4	68.9	10.6	10.9
2-Phenoxyethyl	84	0.2	92	1.5200	1.1037	52.23	52.94	192.2	193.4	68.7	69.2	6.3	6.4
2-Benzyloxyethyl	118	2.3	68	1.5075	1.0741	56.84	57.20	206.2	208.1	69.9	69.8		
2-(*p*-*tert*-Butylphenoxy)ethyl	117	0.1	83	1.5093	1.0326	70.70	71.84	248.3	242.1	72.5	71.7		
2-(2,4-Di-*tert*-amylphenoxy)ethyl[b]	165	0.8	80	1.4905^54°^	0.9612^54°^	98.41	100.10	332.5	335.6	75.9	76.5	9.7	9.8
2-(2-Methoxyethoxy)ethyl	86	4.6	61	1.4392	1.0421	43.62	43.98	174.2	175.6	55.2	55.2	8.1	8.2
2-(2-Ethoxyethoxy)ethyl	45	0.15	78	1.4390	1.0145	48.23	48.80	188.2	188.6	57.4	57.4		
2-(2-Butoxyethoxy)ethyl	103	2.3	81	1.4394	0.9821	57.47	57.97	216.3	214.6	61.1	61.1		
2-(2-Phenoxyethoxy)ethyl	118	0.3	80	1.5108	1.1103	63.11	63.74	236.3	240.0	66.1	66.1	6.8	6.8
2-Isopropoxyethyl[c]	73	6	65	1.4278	0.9430	46.59	46.97	172.2	173.9	62.8	62.9		
Tetrahydrofurfuryl[d]	87	9	91	1.4580	1.0643	39.77	40.05						
Tetrahydrofurfuryl[c]	52	0.4	86	1.4585	1.0435	44.39	44.54	170.2	169.2	63.5	63.6		
p-Methoxybenzyl	100	0.1	67	1.5260	1.1061	52.23	53.34	192.2	194.0	68.7	69.2	6.3	6.5

[a] Brittle points of the polymers were: Methoxyethyl, −25°; ethoxyethyl, −40°; isopropoxyethyl, −28°; and butoxyethyl, −54°. [b] Melting point, 42°. [c] Methacrylate. [d] Previously reported by Claborn (8).

temperature. This indicated that an oxidation reaction was involved; hence it seemed likely that the ether linkage in the alcohol radical was responsible. In accord with this theory, it was found that polyvinyl isopropyl ether and polyvinyl *n*-butyl ether could be air-cured, though the latter reacted slowly.

A series of copolymers of isopropoxyethyl and isobutyl acrylates containing various percentages of the isobutyl ester was prepared. When cured at 100°, with a trace of cobalt octoate, the rate of cure was roughly inversely proportional to the percentage of isobutyl acrylate in the copolymer. It was noted, however, that pure isobutyl polyacrylate could be cured by baking, though the rate was low. Following this surprising result, it was found that methyl, butyl, and 4-methyl-2-pentyl polyacrylates could be air-cured. On the other hand, cyclohexyl polyacrylate, methyl and *n*-butyl polymethacrylates, polystyrene, polyvinyl acetate, and glyceryl phthalate showed no perceptible rate of cure. It has been reported (7) that ethyl polyacrylate can be cured with benzoyl peroxide.

Quantitative comparison of the rates of cure of the various resins is difficult, but the following generalizations appear justified: (a) the presence of an ether linkage enormously increases the rate of cure, and with two ether linkages in the repeating unit the rate is even higher than with one; (b) compounds having branched alkyl groups have a higher rate of cure than those containing only straight chains; (c) the presence of aromatic groups lowers the rate of cure; (d) polyacrylic esters cure faster than polymethacrylic esters, especially in the absence of ether linkages; (e) peroxides and cobalt salts, especially the latter, greatly increase the rate of cure. In the absence of catalysts, only the polyacrylates and polymethacrylates of the ether-alcohols could be cured at a perceptible rate.

The mechanism of the curing process is largely unknown. The fact that it occurs only in the presence of oxygen and is catalyzed by oxidation catalysts indicates that it is an oxidation reaction. Further evidence is furnished by the elementary analysis of the cured resin. An unsupported film of isopropoxyethyl acrylate was highly cured by baking for several days at 150°. The elementary analysis then showed that, on the basis of unchanged carbon content, each monomer unit had lost two hydrogen atoms and gained 1.3 oxygen atoms.

Properties of the cured resins. The cured films were hard, smooth, glossy, clear, transparent, light colored, and flexible. They showed excellent adhesion to wood, glass, and metals, with little or no effect after prolonged immersion in toluene, hexane, acetone, or ethyl acetate. Water and ethyl alcohol produced some swelling and softening of the films but did not loosen them or produce any permanent visible change. Dilute alkaline solutions, such as a 1% solution of sodium carbonate or even soapy water, attacked the cured films vigorously and dissolved or disintegrated most of them within 10 to 15 minutes. This sensitivity to alkali appeared to be proportional to the degree of cure. Highly cured films were partially or wholly dissolved by aqueous alkali, and from such solutions a gummy precipitate could be recovered by acidification. From these observations, it appears that alkali degrades the cured resin in some way that

produces carboxyl groups. That this is not saponification of the acrylate ester groups is shown by the fact that the uncured resin is resistant to alkali, and also by the fact that resins, such as the vinyl ethers, which contain no ester groups show similar alkali sensitivity. All air-cured polymers, including the alkyl acrylates, behaved similarly.

Even highly cured films retained excellent toughness and flexibility. Thus, an unsupported film of isopropoxyethyl polyacrylate baked for 24 hours at 100° could be folded and creased without cracking. Cured films stored at room temperature for 3 years showed no visible change.

EXPERIMENTAL

Alcohols. Most of the alcohols used are commercially available; before they were used they were fractionally distilled. Because commercial methyl and ethyl monoethers of diethylene glycol (Methyl Carbitol and Carbitol) contain considerable glycol, purification by distillation is difficult, particularly with the latter compound. We are indebted to the Carbide and Carbon Chemicals Corporation for a glycol-free sample of Carbitol which was used in the present work; to Sharples Chemicals, Inc. for 2,4-di-*tert*-amylphenoxyethanol, and to Dow Chemical Company for *p*-*tert*-butylphenoxyethanol.

Monomeric esters. The acrylic and methacrylic esters were prepared by the alcoholysis of the methyl or ethyl ester (2–6). The ethyl ester is preferred for making acrylic esters because (a) it has a higher boiling point than methyl acrylate; hence a higher reaction temperature and faster reaction are obtained by its use; (b) the ethanol-ethyl acrylate azeotrope contains much less ester than the methanol-methyl acrylate azeotrope (5); and (c) the wider spread in boiling point between the ester and its azeotrope (32° for ethyl and 17° for methyl) facilitates the distillation of the azeotrope without unnecessary loss of ester in the distillate (5).

Premature polymerization in the still-pot or fractionating column was sometimes troublesome, especially if glycol was present. When exposed to air, both the acrylic esters and the ether-alcohols readily form peroxides which catalyze polymerization; hence the starting materials should be freshly distilled. Air should be rigidly excluded from the still throughout the operation. It was found helpful to pass a fine stream of carbon dioxide into the still-pot through a capillary bubbler tube during the distillation. The monomers were clear, colorless liquids which could be stored indefinitely without inhibitors if kept in a refrigerator at 0–5°. Table I shows yields and other data on the monomers.

Many of these compounds were difficult to analyze for carbon and hydrogen because of frequent explosions in the combustion tube. Although samples of only about 15 to 20 mg. were used, in several instances the tube was shattered by the explosion. Probably this behavior was due to formation of peroxides by the action of oxygen on the ether-esters. In several instances carbon was determined by wet oxidation. We are indebted to C. O. Willits, C. L. Ogg, and their associates, the Analytical and Physical Chemistry Division of this Laboratory for analyses.

Polymerization. The usual procedure was to dissolve 25 g. of monomer and 0.125 g. of benzoyl peroxide in 50 g. of ethyl acetate and boil the solution under a reflux condenser. Polymerization began immediately and resulted in vigorous refluxing for a few minutes. Refluxing was continued for 3 hours, though there was no visible change after 15 to 20 minutes.

Most of the monomers when polymerized in emulsion gave polymers which were insoluble, or only partially soluble, in organic solvents. The acrylates of glycol monoalkyl ethers thus polymerized were soft and rubbery, although not especially tacky. All the acrylates of monoethers of diethylene glycol gave gelled, insoluble polymers.

PHILADELPHIA 18, PA.

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[Contribution from National Cancer Institute, National Institutes of Health]

THE USE OF SODIUM HYDRIDE IN THE ALKYLATION OF N-SUBSTITUTED AMIDES

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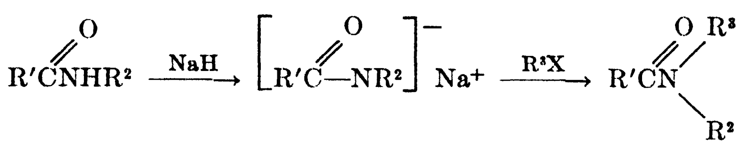
In connection with experiments under way in this laboratory the preparation of certain N,N-di-substituted amides was necessary. A number of examples are recorded in the literature in which compounds of this type have been prepared by the alkylation of an alkali salt of the appropriate N-substituted amide or sulfonamide (1–8). The salts have usually been prepared by the reaction of the N-substituted amide with either metallic sodium, (1, 7, 8) or with alcoholic or aqueous alkali as in the case of the sulfonamides (3, 5, 6) and some formanilides (2).

The use of sodium offers the advantage of the reaction being carried out in a non-hydrolytic solvent. It was thought that the employment of sodium hydride would also offer this advantage and at the same time would be safer and easier to handle than the metal. With this in mind the preparation of a number of N,N-disubstituted amides by the general reaction shown in Equation 1 was undertaken. The results are summarized in Table I.

1. 

From the table it can be seen that when R′ and R^3 were methyl and R^2 was aryl yields of 70–89% were obtained. Similar experiments in which R^2 was *p*-nitrophenyl failed to give any N-methyl-*p*-nitroacetanilide. This failure was apparently one in which the sodium hydride did not react with the amide because after six hours refluxing of the two in xylene the amide was recovered unchanged merely by cooling the reaction mixture.

To study the effect of changes in R^3 on the yield acetanilide was chosen as the starting material. From the table it can be seen that when R^3 was primary, allyl, or secondary the yields were 79%, 73%, and 53% respectively. When *tert*-butyl bromide was used as the halide none of the desired amide was obtained. The decrease resulting as one goes from primary to secondary to tertiary is to be expected and is in accord with well known similar effects in the Gabriel synthesis.

Only one example was tried in which both R′ and R^2 were phenyl and in that case with R^3 methyl a 62% yield of N-methylbenzanilide was obtained.

When the reaction was run on benzenesulfonamide with R^3 as methyl only about 50% of impure product was obtained and 40% of the starting material was recovered. Similarly the reaction failed with phthalimide as starting material and R^3 as methyl, there being obtained a little impure substance which was not further purified and no attempt was made to recover any phthalimide. In

both of these cases the expected alkali salt seemed to form fairly readily but failed to react with the halide to any appreciable extent.

TABLE I

ALKYLATION EXPERIMENTS

R'	R^2	R^3X	PRODUCT	YIELD, %	M.P. OR B.P., °C.	LIT. VALUE
Methyl	Phenyl	Methyl iodide	N-Methylacetanilide	89	98.5–101	101–102[a]
Methyl	α-Naphythl	Methyl iodide	N-Acetyl-N-methyl-α-naphthylamine	82	95–97	95[b]
Methyl	*p*-Chlorophenyl	Methyl iodide	N-Methyl-*p*-chloroacetanilide	72	92–93	92[c]
Methyl	*o*-Anisyl	Methyl iodide	N-Acetyl-N-methyl-*o*-anisidine	79	52–54	51–53[e]
Methyl	*p*-Anisyl	Methyl iodide	N-Acetyl-N-methyl-*p*-anisidine	81	57–59	57–58[d]
Methyl	*p*-Phenylazophenyl	Methyl iodide	N-Acetyl-N-methyl-*p*-aminoazobenzene	72	92–94.5[f]	
Methyl	Phenyl	Butyl bromide	N-Butylacetanilide	79	121–125/4	273–275[g]/718
Methyl	Phenyl	Isopropyl bromide	N-Isopropylacetanilide	53	40–43	(39[h])
Methyl	Phenyl	Allyl bromide	N-Allylacetanilide	73	99–103[i]/2	
Phenyl	Phenyl	Methyl iodide	N-Methylbenzanilide	62	58–59	63[j, k]
Methyl	Methyl	Methyl iodide	N,N-Dimethylacetamide	69	164–167	165–175[l]
Methyl	Butyl	Butyl bromide	N,N-Dibutylacetamide	73	241–244	243–245[m]

[a]Hepp, ref. (1). [b]Norton and Livermore, *Ber.*, **20**, 2272 (1887). [c]Chattaway and Orton, *J. Chem. Soc.*, 465 (1901). [d]Thielepape, ref. (8). [e]Ingold and Ingold, *J. Chem. Soc.*, 1310 (1926). [f]*Anal.* Calc'd for $C_{15}H_{15}N_3O$: C, 71.1; H, 5.9; N, 16.6. Found: C, 71.3; H, 6.2; N. 16.6. [g]Kahn, *Ber.*, **18**, 3365 (1885). [h]Pictet and Crepieux, ref. (2). [i]*Anal.* Calc'd for $C_{11}H_{13}NO$: C, 75.4; H, 7.4; N, 8.0. Found: C, 75.1; H, 7.6, N, 8.1. [j]Hess, *Ber.*, **18**, 685 (1885). [k] The melting point 58–59° was also obtained for the same compound prepared by benzoylating N-methylaniline. [l]Mitchell and Reid, *J. Am. Chem. Soc.*, **53**, 1879 (1931). [m]Dermer and Fernelius, *Z. anorg. u. allgem. Chem.*, **221**, 83 (1934).

In the two instances where R^2 was alkyl instead of aryl the yield of N,N-dialkylamide was somewhat lower.

Of the compounds prepared only N-allylacetanilide and N-acetyl-N-methyl-

p-aminoazobenzene[1] were new. The first was characterized by analysis and hydrolysis to N-allylaniline which was identified as the monoxalate (9). The N-acetyl-N-methyl-*p*-aminoazobenzene was analyzed and hydrolyzed to the known N-methyl-*p*-aminoazobenzene (10).

In the preparation of N-methylacetanilide from acetanilide, sodium hydride, and methyl iodide, either ligroin (b.p. 90–120°) or benzene could be used with equal success as a solvent, but when sodium hydride and N-acetyl-α-naphthylamine were refluxed twenty-four hours in benzene no apparent reaction occurred. However, if xylene was used as the solvent a good yield of the desired compound was obtained by alkylation of the intermediate sodio derivative. As a result of this observation xylene was used as the solvent in the remaining experiments except for those run on methylacetamide and phthalimide. Benzene was used as a solvent for the former because of the proximity of the boiling point of the product to that of xylene and phenetole was used for phthalimide because of the slight solubility of the latter in xylene.

In the experiment using acetanilide two hours refluxing was sufficient to bring about complete formation of the sodium salt but in the case of some of the other compounds, *e.g.* N-acetyl-*o*-anisidine, overnight refluxing led to improved yields.

EXPERIMENTAL[2, 3, 4, 5]

Since all of the reactions were carried out in similar ways, complete directions will be given only for the preparation of N-acetyl-N-methyl-*p*-anisidine.

N-Acetyl-N-methyl-p-anisidine. Into a dry three-necked round-bottomed flask, equipped with stirrer, reflux condenser, and addition funnel there was introduced 1.4 g. of sodium hydride and 50 ml. of xylene which had been dried over sodium. There was then added 8.3 g. of N-acetyl-*p*-anisidine in 200 ml. of boiling xylene and the mixture was refluxed with stirring for twenty hours, under an atmosphere of nitrogen, during which time the white sodium salt precipitated.

After the reaction had been allowed to cool the reflux condenser was replaced by a Dry Ice-acetone condenser; 20 g. of methyl iodide was added and the reaction mixture was refluxed eight hours more. The hot mixture was filtered; the residue was washed with 50 ml. of dry benzene and the washings added to the original filtrate. Stripping of the solvent followed by distillation yielded 8.0 g. of material, b.p. 137–140° at 3.5 mm., m.p. 50–56°. One recrystallization from ligroin (b.p. 90–120°) gave 7.3 g. (80%) of N-acetyl-N-methyl-*p*-anisidine, m.p. 57–59°.

N-Allylaniline. N-Allylacetanilide (9.5 g.) was refluxed in 50 ml. of 3 *N* hydrochloric acid for two hours. Isolation of the product in the usual manner gave 5.4 g. of N-allyl-

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[1] Berju, *Ber.*, **17**, 1400 (1884), reported the preparation of this compound and gave m.p. 139°. However, the starting material he used, supposedly N-methyl-*p*-aminoazobenzene, had m.p. 180° and in view of the discrepancy between this and the accepted value [88–88.5° (10)] the product obtained by its acetylation could not have been the reported N-acetyl-N-methyl-*p*-aminoazobenzene.

[2] All melting points corrected.

[3] Analysis by R. J. Koegel of this laboratory.

[4] The yields in these experiments are not necessarily optimum since conditions for the reactions were not studied sufficiently to make a statement on that point.

[5] We are indebted to the Electrochemicals Department of E. I. du Pont de Neumours Co. for the sodium hydride used in these experiments.

aniline, b.p. 70–80°/2 mm., and 1.2 g. of N-allylacetanilide was recovered. Redistillation of the N-allylaniline yielded 4.7 g. (63%), b.p. 62–65°/1.2 mm.

N-Allylaniline oxalate. N-Allylaniline (1.75 g.) in 25 ml. of ether was added to 1.3 g. of oxalic acid dihydrate in 100 ml. of ether. The salt began to separate immediately and after one hour the solution was filtered giving 1.6 g. (60%) of the oxalate, m.p. 120–122°, [lit. (9) 120°]. Concentration of the mother liquors yielded another 0.4 g., m.p. 115–118°.

Anal. Calc'd for $C_{11}H_{13}NO_4$: C, 59.2; H, 5.8.

Found: C, 59.1, 59.3: H, 5.7, 6.0.

N-Methyl-p-aminoazobenzene. Two g. of N-acetyl-N-methyl-*p*-aminoazobenzene was refluxed six hours in a mixture of 35 ml. of alcohol and 30 ml. of 6 *N* hydrochloric acid. The solution was made alkaline, cooled, and the resulting precipitate collected by filtration. This was twice recrystallized from ligroin (b.p. 90–120°) to give 1.53 g. (92%) of N-methyl-*p*-aminoazobenzene, m.p. 86.4–88.6° [lit. (10) 88.0–88.5°].

SUMMARY

A number of N,N-dialkyl amides have been prepared by the action of sodium hydride and an alkyl halide on an N-alkyl amide.

Two new substituted amides, N-allylacetanilide and N-acetyl-N-methyl-*p*-aminoazobenzene were prepared and characterized during the course of the experiments.

BETHESDA 14, MARYLAND

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AN IMPROVED SYNTHESIS OF DL-GLYCERALDEHYDE

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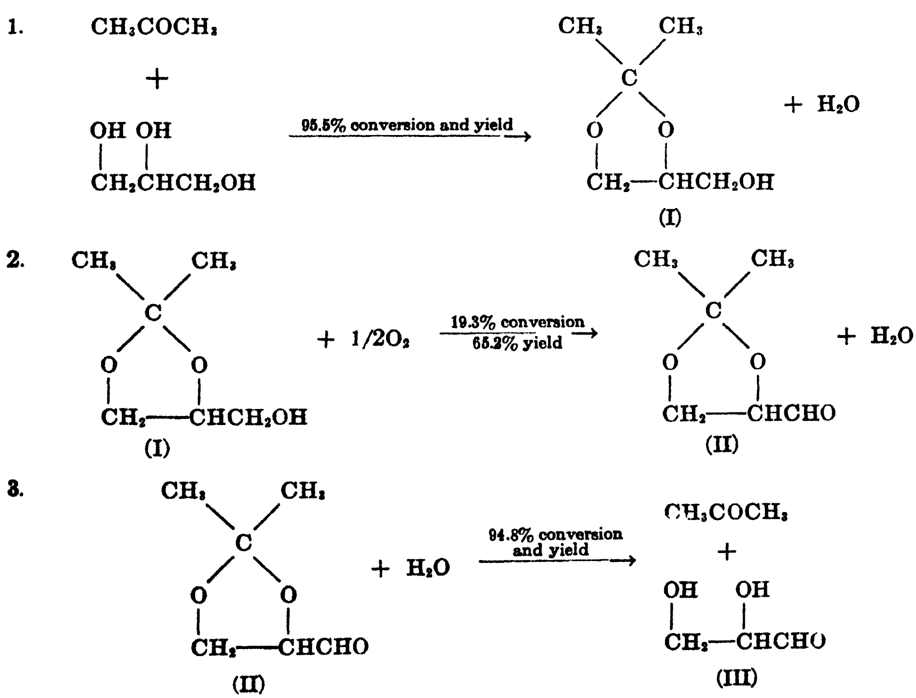
Announcement (1) that DL-glyceraldehyde (III) might be an effective inhibitor of dental caries prompted attempts in these laboratories to find an attractive method for its synthesis. It is the purpose of this paper to report the synthesis which was developed during this work.

The best literature method for the synthesis of DL-glyceraldehyde appears to be that of Organic Syntheses (2), in which acrolein is prepared by dehydrating glycerol and then is converted to β-chloropropionaldehyde diethyl acetal, which is dehydrochlorinated to acrolein diethyl acetal. The latter is oxidized with potassium permanganate to give DL-glyceraldehyde diethyl acetal, which is hydrolyzed with dilute acid to yield DL-glyceraldehyde. The method is cumbersome, and the over-all conversion from glycerol to DL-glyceraldehyde is only 6.6%.

Our synthesis is a three-step procedure in which the over-all conversion (based on reactants charged) from glycerol to DL-glyceraldehyde is 17.5% and the over-all yield (based on reactants consumed is 59%. The new method involves protecting two of the hydroxyl groups of glycerol by ketal formation, catalytically air-oxidizing the resulting monohydric alcohol to the corresponding aldehyde, and hydrolyzing the product to form glyceraldehyde.



The method is based on the demonstration by Fischer (3) and by Hibbert and Morazain (4) that the reaction product of acetone and glycerol is the 1,2-adduct, 2,2-dimethyl-4-hydroxymethyl-1,3-dioxolane (I). This material was synthesized in 95.5% conversion and yield by a modification of the method of Newman and Renoll (5). The stirring and the filtration of neutralized catalyst were omitted and 0.005% sulfuric acid catalyst was employed instead of 0.5% *p*-toluenesulfonic acid. Methylene chloride was used as the water carrier instead of petroleum ether in order to minimize the fire hazard.

Air oxidation of (I) (Step 2) has not been reported previously. The product, 2,2-dimethyl-4-formyl-1,3-dioxolane (II), has been synthesized by Baer and Fischer (6), and its acid-catalyzed hydrolysis was carried out by Baer, Grosheintz, and Fischer (7) without isolation of either the reactant or the product. It has now been found that the hydrolysis (Step 3) can be carried out without a catalyst; this procedure greatly simplifies the isolation of pure glyceraldehyde.

EXPERIMENTAL PART

Source of materials. Two grades of glycerol were tested as received from Colgate-Palmolive-Peet Co. Water-white U.S.P. glyercol gave poorer results than yellow, high-gravity glycerol (minimum specific gravity, 1.2620 at 15.6°/15.6°). A C.P. grade of acetone from Carbide and Carbon Chemicals Corp. was used as received. C.P. concentrated sulfuric acid and methylene chloride were products of E. I. duPont de Nemours and Co., Inc. Anhydrous sodium formate was purchased from Mallinckrodt Chemical Works, and the absolute alcohol used was the U.S.P. grade from U. S. Industrial Chemicals, Inc. Electrolytic hydrogen of 99.9% purity was purchased from Paschall Oxygen Co., and compressed air was obtained in cylinders from Air Reduction Sales Co. The latter company provided deoxidized, oil-pumped, and dried nitrogen. Distilled water was used at all times.

2,2-Dimethyl-4-hydroxymethyl-1,3-dioxolane (I). A mixture of 900 g. of yellow high-gravity glycerol, 2 liters of acetone, 1 liter of methylene chloride, and 0.1 cc. of concentrated sulfuric acid was refluxed continuously for 55 hours under a 3′ × 1″ Fenske packed column. The column's head was adjusted to withdraw the water of reaction and return the methylene chloride layer as reflux. At the end of the processing time, 0.5 g. of sodium formate was added and the mixture was distilled in a grease-free all-glass Vigreux column. The product (I) was distilled rapidly at 189–190.5° at atmospheric pressure. The conversion to distilled product was 94.4%; a sixty-eight hour run gave 95.5% conversion. The product was redistilled at atmospheric pressure prior to use in the oxidation step.

The boiling point of 2,2-dimethyl-4-hydroxymethyl-1,3-dioxolane is 188–189°/760 mm., or 80.5–80.8°/11 mm. Its refractive index at 25° is 1.4326, and the specific gravity of the colorless oil is 1.055 at 25°.

Although the reaction mixture for Step 1 was originally heterogeneous, stirring was found unnecessary. Yellow, high-gravity glycerol repeatedly gave conversions of greater than 90%, while the best conversion obtained with water-white U.S.P. glycerol was 88%. Attempts were made to hasten the reaction by using larger quantities of sulfuric acid catalyst. However, the reaction was no faster and the yield became lower as the quantity of catalyst was increased. In the absence of a catalyst the reaction was too slow to be practical.

2,2-Dimethyl-4-formyl-1,3-dioxolane (II). The Pyrex glass converter (Fig. 1) was equipped with an unpacked spiral tube to preheat the gases and a section packed with 4–6 mesh quartz for vaporizing and preheating (I). The quartz had been digested with nitric acid at 100°, washed with water, and ignited at 700°. Several chromel-alumel thermocouples were located in the catalyst bed. The reactor, which was enclosed in an electric furnace with automatic temperature control, was placed behind a steel barricade. No explosions occurred. The liquid feed was either dropped into the converter from an ungreased dropping-funnel,

or pumped with a brass and bronze bellows pump (Precision Scientific Co., #9000) through copper tubing. Nitrogen and air were metered and introduced through glass tubing connected with washed gum rubber tubing. The gases were purified by passage over dehydrated Davison silica gel at room temperature.

The catalyst was prepared by impregnating tabular alumina with aqueous silver nitrate. A solution of 50 g. of silver nitrate in 36 cc. of distilled water was added to 100 cc. of 8–14 mesh Alorco T-61 tabular alumina with stirring. Excess solution was drained off by spreading the solid particles on filter paper and the catalyst was dried for four hours in a 110° oven.

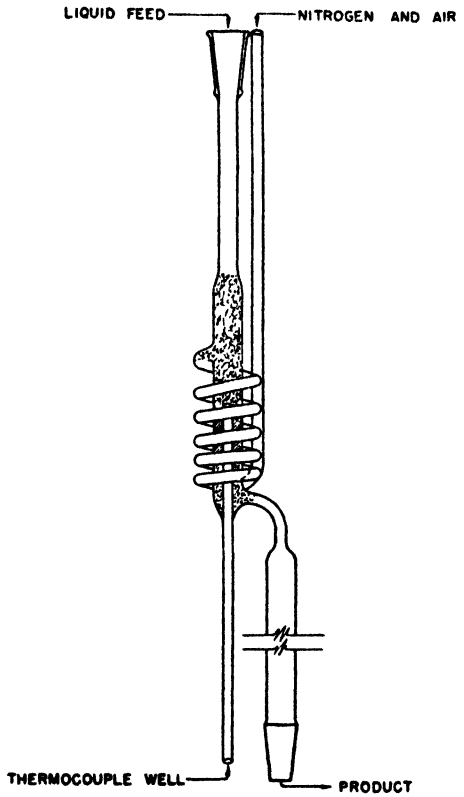


FIGURE 1. CONVERTER FOR OXIDATION REACTION

The catalyst (8 cc.) was reduced in place with a nitrogen-hydrogen mixture and finally with pure hydrogen at 350°. After hydrogen had been displaced from the apparatus with nitrogen, oxidation was started using air as the oxidizing agent. After the reaction started it was necessary to dilute the air with added nitrogen to keep the maximum catalyst temperature at about 410°. The reactor effluent was cooled and the condensate was collected. Uncondensed gas was passed through Dry Ice traps prior to metering and analysis with an Orsat apparatus.

In one experiment a total of 772 cc. (815 g.) of (I) was oxidized at a hot spot temperature of about 410°, using an average space velocity (cc. gas, calculated at STP/cc. catalyst/hr.) of 1475 $hr.^{-1}$ for (I), an average air space velocity of 3500 $hr.^{-1}$ and an average nitrogen space velocity of 3600 $hr.^{-1}$. The total condensate, which weighed 879.2 g., was kept cold overnight and was then distilled through a 3′ × 1″ Vigreux column, starting at 100 mm. pressure.

After the removal of water, 204.8 g. of crude 2,2-dimethyl-4-formyl-1,3-dioxolane (II) was distilled at 93–114° at 102–108 mm., followed by 556.5 g. of recovered (I) boiling at 76.5–80°/10 mm. The residue weighed 25.4 g. The crude product was redistilled, giving 154.8 g. of pure (II) and 18 g. of starting material. Thus the conversion to pure (II) was 19.3%, and the yield was 65.2%. The straw-yellow product boiled at 74°/50 mm., and a freshly distilled sample had a refractive index at 25° of 1.4189. The refractive index and the viscosity increased with the age of the sample, probably due to trimerization. A purified sample had a total carbonyl number (8) of 841 (theory 876). The catalyst showed a life of 13–44.5 hours. The longer life was demonstrated using recovered (I) that was recycled after two redistillations. Dow-Corning (silicone) stopcock grease seemed to destroy the activity of the catalyst. For this reason no grease was allowed to come in contact with (I), either in the still or in the oxidation apparatus. Instead, the alcohol itself was used as the lubricant for ground glass joints and stopcocks in the purification and oxidation apparatus.

The nitrogen-air mixture entering the converter ordinarily contained about 10% oxygen; the off-gas usually analyzed about 1% oxygen, 1–5% carbon dioxide, and 0.3–2% carbon monoxide.

DL-*Glyceraldehyde (III)*. To 200 cc. of water at 10° was added 49.5 g. of freshly distilled 2,2-dimethyl-4-formyl-1,3-dioxolane (II). The temperature spontaneously rose to 20°. In this experiment an attempt was made to carry out the hydrolysis at room temperature, removing the acetone at 50 mm. pressure. However, the reaction was not complete at room temperature and was finished by refluxing for 3.5 hours at a bath temperature of 40–60°. The water was evaporated from the solution at room temperature and low pressure. Three days later most of the water had been removed, leaving a thick colorless syrup containing some crystals. An equal volume of absolute ethanol was added. Five days later the crystals were removed by vacuum filtration and washed with absolute alcohol. The conversion to the first crop of crystals was 53.6%. The filtrate was evaporated at room temperature and low pressure; additional absolute alcohol was added occasionally. Two weeks after the first filtration a second filtration was carried out, yielding an additional quantity of finely powdered, crystalline, white DL-glyceraldehyde, and after three more weeks a third crop was collected. The total conversion to the three crops was 92%. A similar experiment resulted in 94.8% conversion to crystalline glyceraldehyde.

In the hydrolysis step, water: 2,2-dimethyl-4-formyl-1,3-dioxolane ratios ranging from 10:1 to 30:1 all gave good results. Also, it was possible to carry out the reaction at 100° at atmospheric pressure, instead of at 50–60° and 50 mm. For example, a 75.3% conversion to crystalline product was obtained in an experiment in which the water:aldehyde ratio was 10:1 and in which the processing conditions were 93–100° at atmospheric pressure for 36 minutes. Another experiment at 100° for 30 minutes gave an 84% conversion. When the water and aldehyde were mixed and allowed to stand overnight prior to heating, only one hour at 50–60°/50 mm. was required instead of 3.5 hours.

When (II) was mixed with water, the mixture was yellow and heterogeneous for about fifteen seconds and then became colorless and homogeneous. During this time the temperature rose, sometimes to 65°.

The white dimeric crystals of DL-glyceraldehyde were small and grew very slowly, from either the syrup or its ethanol solution. The yield of crystals was diminished by overheating of the glyceraldehyde, especially in the absence of a diluent. For this reason the glyceraldehyde was not heated above room temperature after the hydrolysis of (II) was completed.

The final product was washed with absolute alcohol and dried at room temperature under reduced pressure. The melting point of DL-glyceraldehyde, when determined in a capillary tube, depended on the rate of heating. For example the melting point of a particular sample fell from 142–142.4° to 134.8–136° when the heating rate was decreased. Various samples of DL-glyceraldehyde melted at temperatures between 167.3° and 185.4° on a Dennis melting point bar (Parr Instrument Co., Model MPB); this technique is known to give higher melting points than the capillary tube method with heat-sensitive substances.

The identity of the glyceraldehyde was confirmed by a mixed melting point with a

sample of DL-glyceraldehyde supplied by Prof. L. S. Fosdick of Northwestern University. In the same bath at the same time, the authentic sample melted at 132.5–133.2°, the experimental sample at 132.5–133.1°, and the mixture at 132–133° (uncorr.). The total carbonyl number (8) of a synthetic product was 639 ± 2 (theory, 623) for a duplicate determination.

Acknowledgments. A sample of DL-glyceraldehyde was very kindly furnished by Prof. L. S. Fosdick of Northwestern University. The skillful laboratory assistance of T. T. Malinowski is gratefully acknowledged. Analyses were performed by the Ammonia Department Analytical Laboratory, under the supervision of J. Mitchell, Jr.

SUMMARY

In a new three-step synthesis of DL-glyceraldehyde from glycerol, two of the hydroxyl groups are protected by ketal formation with acetone. The product is then catalytically oxidized with air to the corresponding aldehyde, which is hydrolyzed to glyceraldehyde without the use of a catalyst. The over-all conversion and yield are 17.5% and 59%, respectively.

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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ARMOUR AND COMPANY]

THE SOLUBILITIES OF THE NORMAL SATURATED FATTY ACIDS IN WATER

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Solubilities of saturated fatty acids in water reported by John and McBain (1) are one-fifth to one-tenth of those reported by Ralston and Hoerr (2). As a result of these discrepancies, it was decided to reopen the study.

EXPERIMENTAL

Preparation of Materials. The fatty acids used in this work were highly purified samples prepared by Mr. R. S. Sedgwick. Freezing points of the acids were as follows: octanoic, 16.63°; nonanoic, 12.52°; decanoic, 31.49°; hendecanoic, 28.59°; dodecanoic, 44.16°; tetradecanoic, 54.25°. Water with a conductivity of 1 micromho was used in making up all solutions.

Procedure. Most of the determinations were made on fatty-acid solutions saturated by heating to 100°, shaking, then placing in a constant-temperature bath with a regulation range of ±0.05°. In several cases, saturation was also approached from a lower temperature, and in all such runs identical values were obtained. The minimum saturation time at the desired temperature was 16 hours. This time was checked in some cases by starting from an over- or under-saturated state, and was found to be adequate. During the saturation period, the solution was stirred by bubbling purified nitrogen through it. The nitrogen had previously been led through soda-lima and then water.

To measure a volume of solution for analysis, a pipet of 149.4 cc. capacity was built into the constant-temperature bath in such a way that most of the path for transporting the solution from the saturation flask to the pipet was in the water-bath. This system was so arranged that the solution was exposed only to the purified-nitrogen atmosphere.

The cell consisted of unplatinized platinum electrodes built into a 300-cc. round flask. The constant was approximately 0.07.

Titrations were performed in a separate water-bath. To prevent possible precipitation in moving the cell, 50 cc. of water was placed in the cell before the solution was added, and the titration bath was always at the saturation temperature or higher. To remove any remaining carbon dioxide from the solution in the cell, nitrogen, freed from carbon dioxide and saturated with water vapor at the titration temperature, was bubbled through the solution for 1 hour before titration. This passage of nitrogen was also used to stir the solution during the titration. The titrations of decanoic and longer-chain acids were run conductometrically. After preliminary trials, using various procedures with a known concentration of dodecanoic acid, it was concluded that by adding an excess of NaOH solution and back-titrating with HCl, the sharpest end-point was obtained. It was found that an excess of at least 1 cc. of 0.02 N base was necessary to give correct results. Lesser excesses of base did not remove all adsorbed acid from the cell walls. Octanoic and nonanoic acids were titrated directly with 0.1 N and 0.02 N NaOH, respectively, at 100°, using phenolphthalein as an indicator.

RESULTS AND DISCUSSION

The solubilities of the fatty acids at several temperatures are shown in Table I and temperature-solubility curves are shown in Figure 1. Attempts to measure the solubility of hexadecanoic and octadecanoic acids yielded values which were

not considered reliable. This is also true of dodecanoic and tetradecanoic acids at the lower temperatures (40° and 30°). Values for the solubility of octanoic acid are in agreement with those previously reported (2).

It is to be noted that alternation in the solubilities of even- and odd-chain-length acids does not occur although it might be expected from the alternation exhibited in melting points and latent heats of fusion. This may be due to the non-ideal nature of the solutions.

At comparable experimental points, our values are of the same magnitude as those of John and McBain (1). We believe that our values are more nearly correct

TABLE I

SOLUBILITIES OF NORMAL SATURATED FATTY ACIDS IN WATER

NO. OF C ATOMS	SOLUBILITY IN G./100 CC. OF SOLUTION			
	30°	40°	50°	60°
8	0.0789	0.0843	0.0943	0.1071
9	.0212	.0222	.0264	.0299
10	.0064	.0072	.0081	.0100
11	.00198	.0023	.0026	.0032
12		.00077	.00092	.00116
14			.00042	.00056

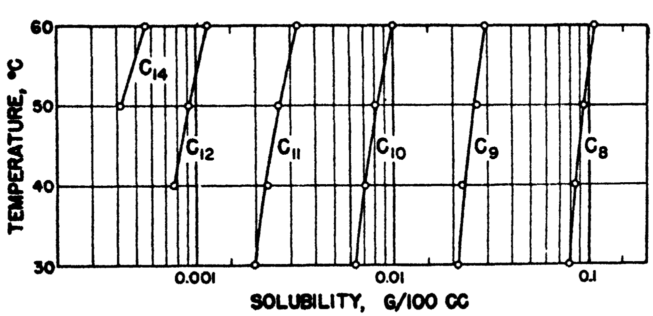

FIGURE 1. SOLUBILITIES OF THE FATTY ACIDS IN WATER

for the reasons following. John and McBain, using a conductivity method, took readings after fifteen minutes even though the resistance was changing owing probably to adsorption. The fact that material was adsorbed would lead to erroneous results. The assumption that their impurity was entirely carbon dioxide may be questioned. The equation $C_{H^+} = C_{P^-} = 4.26 \times 2.35 \times 10^{-12} = 3.16 \times 10^{-6}\ M$ is also not justified. In our work, acid adsorbed on the walls was removed by a proper excess of NaOH. Carbon dioxide was also removed, and the method is in general a more direct one.

Acknowledgment. The authors wish to acknowledge valuable suggestions made by Dr. I. M. Kolthoff in the course of this work.

SUMMARY

The solubilities of octanoic, nonanoic, decanoic, and hendecanoic acids were determined in water at 30°, 40°, 50°, and 60°; of dodecanoic acid at 40°, 50°, and 60°, and of tetradecanoic acid at 50° and 60°.

CHICAGO, ILLINOIS

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[CONTRIBUTION FROM THE B. F. GOODRICH RESEARCH CENTER]

SYNTHESIS OF DERIVATIVES OF 4,5-DIMETHYL-2-MERCAPTOTHIAZOLE

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Thiazoles, particularly 2-mercaptobenzothiazole, and certain derivatives of these compounds, have found wide application as accelerators for the vulcanization of rubber. This investigation had for its purpose the synthesis of a series of derivatives of 4,5-dimethyl-2-mercaptothiazole to determine the effect of different substitutents on the properties of rubber vulcanizates. A comparison of the activity of these compounds as vulcanization accelerators will be reported elsewhere.

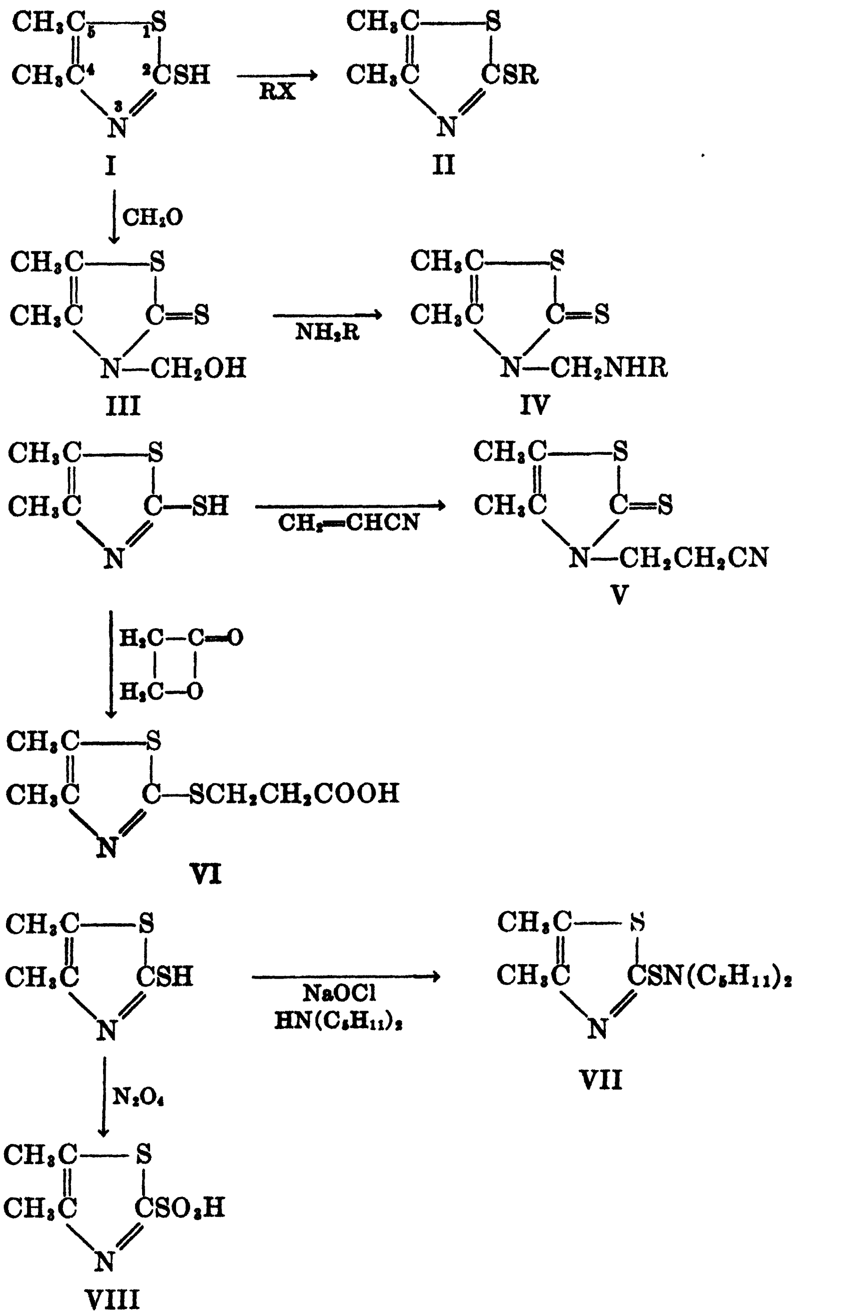
Derivatives prepared from the parent 4,5-dimethyl-2-mercaptothiazole (I) in this study can be broadly classified into several groups. Members of the largest class (II) were synthesized by reacting the sodium salt of 4,5-dimethyl-2-mercaptothiazole, either in water solution or as the anhydrous sodium salt, with the following halogenated reagents: *n*-butyl bromide, benzyl chloride, 1,4-dichlorobutane, 2-chloroethylamine, 2,4-dinitrochlorobenzene, chloroacetone, chloroacetamide, benzoyl chloride, phthalyl chloride, furoyl chloride, *o*-nitrobenzenesulfenyl chloride, and 2-chloro-6-nitrobenzothiazole. The lead, magnesium, and zinc salts of I were similarly prepared from water-soluble salts of the corresponding metals.

The hydroxymethyl derivative (III) was obtained by reacting I with formaldehyde and this compound was further condensed with amines to form aminomethyl derivatives (IV). While three members of this class, compounds derived from *p*-phenylenediamine, *n*-butylamine, and *o*-toluidine were isolated, only the one derived from the latter amine was stable to recrystallization. Under the experimental conditions employed, attempts to prepare similar derivatives from diethylamine, cyclohexylamine, and *n*-amylamine were unsuccessful.

Acrylonitrile reacted with I to produce the cyanoethyl derivative (V), while with β-propiolactone a high yield of the substituted propionic acid (VI) was obtained. A member of the sulfenamide class (VII) was prepared from diamylamine.

Oxidations were performed to produce the previously described 4,5-dimethylthiazole and the disulfide, 2,2′-dithiobis-(4,5-dimethylthiazole) (1). The sulfonic acid (VIII) was obtained by oxidation of I with nitrogen tetroxide under mild reaction conditions.

Unpublished results of ultraviolet absorption studies performed in these laboratories show that the substituting radical in compounds III, IV, and V is attached to the nitrogen rather than to the sulfur of the thiol group. In the preparation of these derivatives, I apparently reacted in a different form, possibly as a tautomer, from that shown structurally. 4,5-Dimethyl-2-mercaptothiazole, in other reactions described in this paper, reacts in a manner to support



I, II, III, IV, V, VI, VII, VIII

the structure given (I). A similar relationship for the derivative of 2-mercaptobenzothiazole corresponding to V has previously been reported (2).

EXPERIMENTAL[1]

Ammonium dithiocarbamate (3). A solution of 152 g. (2 moles) of carbon disulfide and 1,000 ml. of dry isopropyl acetate was vigorously agitated in a reaction flask. Ammonia (68 g., 4 moles) was introduced in a gaseous form below the liquid surface while maintaining the reaction mixture at 20–30°. The pale yellow, rather unstable product which precipitated was recovered by filtration, and after drying rapidly at room temperature (203 g.), was stored in a refrigerator. An alternative method was to add water to the slurry of ammonium dithiocarbamate in isopropyl acetate and recover the product as a water solution. A water solution of ammonium dithiocarbamate, which should also be stored in a refrigerator, is more stable than the dry product.

4,5-Dimethyl-2-mercaptothiazole (I). This compound (4) was prepared by reacting ammonium dithiocarbamate with a mixture of 3-chloro-2-butanone and 1-chloro-2-butanone which was obtained by the chlorination of 2-butanone. To a solution of 121 g. (1.1 moles) of ammonium dithiocarbamate in 500 ml. of water there was rapidly added 106.5 g. (1 mole) of mixed monochlorobutanones. The reaction mixture was agitated vigorously, the temperature rose to about 90°, and a finely divided solid precipitated. The product weighed 123 g. (85% yield). The mixture of 4,5-dimethyl-2-mercaptothiazole and 4-ethyl-2-mercaptothiazole resulting from this reaction was extracted with sodium carbonate to dissolve the latter compound. 4,5-Dimethyl-2-mercaptothiazole, which represented about 80% of the mixture, was recovered by filtration. As further purification it was extracted twice with benzene to give 4,5-dimethyl-2-mercaptothiazole melting at 162–163° (1).

Anhydrous sodium salt of 4,5-dimethyl-2-mercaptothiazole (IX). Twelve grams (0.5 mole) of sodium metal was slowly added to 500 ml. of ethanol. To the solution of sodium ethoxide was added 72.5 g. (0.5 mole) of I. Ethanol was removed from the resulting solution by evaporation and the salt was stored under anhydrous conditions.

4,5-Dimethyl-2-n-butylmercaptothiazole. To 83.5 g. (0.5 mole) of IX dissolved in 400 ml. of ethanol, 68.5 g. (0.5 mole) of *n*-butylbromide was added dropwise, with agitation. The reaction mixture was heated under reflux for 2 hours and was filtered to remove sodium bromide. After evaporation of ethanol, 85 g. of the liquid product was recovered.

4,5-Dimethyl-2-benzylmercaptothiazole. A solution of 33.4 g. (0.2 mole) of IX in 300 ml. of methanol was heated under reflux with 25.2 g. (0.2 mole) of benzylchloride for 1 hour. Sodium chloride was removed, and after concentrating the filtrate, there was obtained 37 g. of the liquid product.

4,5-Dimethyl-2-(4-chlorobutylmercapto)thiazole. A solution consisting of 83.5 g. (0.5 mole) of IX, 32 g. (0.25 mole) of 1,4-dichlorobutane, and 350 ml. of ethanol was heated under reflux for 2 hours. The reaction mixture was filtered and ethanol was evaporated from the filtrate to yield 50 g. of the liquid product.

3-β-Cyanoethyl-4,5-dimethyl-2-thiono-4-thiazoline. To a solution of 72.5 g. (0.5 mole) of I in 200 ml. of 10% aqueous sodium hydroxide there was added dropwise, with agitation, 26.5 g. (0.5 mole) of acrylonitrile. After stirring for 11 hours at room temperature, the crude product was 21 g. of crystalline material. This compound was purified by recrystallization from ethanol.

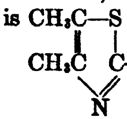
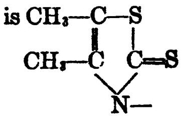
4,5-Dimethyl-2-(2-aminoethylmercapto)thiazole (*5*). Seventy-two and one-half grams (0.5 mole) of I, dissolved in 400 ml. of 10% aqueous sodium hydroxide, was added to 58 g. (0.5 mole) of 2-chloroethylamine hydrochloride dissolved in 100 ml. of water. The agitated solution was heated at 85° for 30 minutes and 58 g. of the liquid product was recovered by extraction with ether.

4,5-Dimethyl-2-(2,4-dinitrophenylmercapto)thiazole. Eighty-one grams (0.4 mole) of 2,4-dinitrochlorobenzene was dissolved in 400 ml. of ethanol and with agitation, was added at 30–35° to a solution of 58 g. (0.4 mole) of I in 200 ml. of 8% sodium hydroxide. The yellow,

[1] All melting points and boiling points reported are uncorrected.

TABLE I

DERIVATIVES OF 4,5-DIMETHYL-2-MERCAPTOTHIAZOLE

R is  R′ is 

DERIVATIVE	YIELD,[a] %	M.P. OR B.P., °C.[b]	EMPIRICAL FORMULA	C, % Calc'd	C, % Found	H, % Calc'd	H, % Found	N, % Calc'd	N, % Found	S, % Calc'd	S, % Found	MOL. WT. Calc'd	MOL. WT. Found
$RS(CH_2)_3CH_3$[c]	84	101	$C_9H_{15}NS_2$	53.73	53.67	7.46	7.48	6.97	7.06	31.84	31.94	201	207
$RSCH_2C_6H_5$[d]	79	173–176	$C_{12}H_{13}NS_2$	61.27	61.10	5.54	5.63	5.96	6.04	27.23	27.32	235	232
$RS(CH_2)_4Cl$[e]	85	115–116	$C_9H_{14}ClNS_2$	45.86	45.59	5.96	6.02	5.96	6.00	27.15	27.18	235	231
$R'(CH_2)_2CN$	22	158–159	$C_8H_{10}N_2S_2$	48.48	48.44	5.06	5.08	14.14	14.06	32.32	32.32	198	203
$RS(CH_2)_2NH_2$[f]	61	115–117	$C_7H_{12}N_2S_2$	44.68	44.67	6.38	6.42	14.90	14.97	34.04	34.04	188	193
RSC_6H_3-2,4-$(NO_2)_2$	97	150–151	$C_{11}H_9N_3O_4S_2$	42.44	42.15	2.89	2.87	13.50	13.39	20.57	20.46	311	307
$R'CH_2OH$	89	75–78	$C_6H_9NOS_2$	41.15	41.25	5.14	5.18	8.00	8.08	36.57	36.64	175	175
$RS(CH_2)_2COOH$	85	66–67	$C_8H_{11}NO_2S_2$	44.24	44.24	5.07	5.13	6.46	6.48	29.49	29.50	217	219
$RSCH_2COCH_3$	91		$C_{14}H_{15}N_5O_4S_2$[g]	44.09	44.07	3.93	3.94	18.38	18.49	16.80	16.87	381	386
$RSCH_2CONH_2$	71	105–106	$C_7H_{10}N_2OS$	41.54	41.56	4.98	5.04	13.86	13.88	31.71	31.76	202	207
$R'CH_2NHC_6H_4$-o-CH_3	90	98–99	$C_{13}H_{16}N_2S_2$	59.07	59.12	6.10	6.00	10.60	10.61	24.23	24.34	264	269
$RSCOC_6H_5$	99	62–63	$C_{12}H_{11}NOS_2$	57.83	57.66	4.42	4.51	5.63	5.68	25.70	25.83	249	247
$(RSCO)_2$-1,2-C_6H_4	87	118–119	$C_{18}H_{16}N_2O_2S_4$	51.43	51.39	3.81	3.81	6.67	6.66	30.47	30.56	420	408
RSCOC:CHCH:CHO	94	90–91	$C_{10}H_9NO_2S_2$	50.19	50.26	3.79	3.68	5.86	5.81				
$RSN(C_5H_{11})_2$[h]	70	138–140	$C_{15}H_{28}N_2S_2$	59.94	58.62	9.39	9.21	9.34	9.84	21.33	22.46	300	281
$RSSC_6H_4$-o-NO_2	89	81–82	$C_{11}H_{10}N_2O_2S_3$	44.29	44.27	3.36	3.45	9.39	9.43	32.23	32.26	298	301
RSY[i]	77	128–129	$C_{12}H_9N_3O_2S_3$	44.56	44.60	2.80	2.79	12.99	12.87	29.77	29.82	323	325
RSO_3H	76	260–263	$C_5H_7NO_3S_2$	31.09	31.16	3.62	3.76	7.25	7.25	33.17	33.17	193	188
RSSR[j]	92	51–52											
RH[k]	60	83–84											

DERIVATIVE	YIELD,[a] %	EMPIRICAL FORMULA	Element	Calc'd	Found
$(RS)_2Pb$	96	$C_{10}H_{12}N_2PbS_4$	Pb	41.81	41.50
$(RS)_2Mg$	87	$C_{10}H_{12}MgN_2S_4$	Mg	7.78	7.57
$(RS)_2Zn$	95	$C_{10}H_{12}N_2S_4Zn$	Zn	18.48	18.59

[a] Yields are based on crude products. [b] Data are for analytical samples. [c] Distilled at 1.0 mm.; n_D^{20} 1.5461. [d] Distilled at 6.0 mm.; n_D^{20} 1.6153. [e] Distilled at 0.4 mm.; n_D^{20} 1.5958. [f] Distilled at 0.9 mm.; n_D^{20} 1.5940. [g] Empirical formula and analysis are for the 2,4-dinitrophenylhydrazone derivative. [h] Distilled at 2 mm. As the material was not very stable to distillation, unsuccessful efforts were made to prepare a derivative such as the picrate and the methiodide for purposes of identification. [i] Y represents the 6-nitrobenzothiazole nucleus. [j] Reported (1) m.p. 51.5°. [k] Distilled at 61 mm. Reported (1) b.p. 81–83° at 59 mm.

crystalline precipitate weighed 120 g., m.p. 145–147°. This compound was purified by recrystallization from ethanol.

3-Hydroxymethyl-4,5-dimethyl-2-thiono-4-thiazoline. One hundred forty-five grams (1 mole) of I and 410 g. (5 moles) of 37% formaldehyde were agitated and heated together at 93–95° for 2 hours. The resulting solution was cooled to 50° and was diluted with 300 ml. of water. The solid precipitated after cooling the mixture to 10°; yield 155 g.

β-(4,5-Dimethyl-2-thiazolyl)mercaptopropionic acid. To a solution of 145 g. (1 mole) of I in 200 ml. of 20% aqueous sodium hydroxide was added, with agitation, 72 g. (1 mole) of β-propiolactone at 20–30°. The mixture was agitated for 30 minutes and was then acidified at 20° with 37% hydrochloric acid. The white, crystalline product (185 g.) was purified by recrystallization from benzene.

4,5-Dimethyl-2-acetonylmercaptothiazole. To a stirred solution of 72.5 g. (0.5 mole) of I in 200 ml. of 10% aqueous sodium hydroxide was added 46.3 g. (0.5 mole) of chloroacetone at 35–45°. After agitating for 1 hour, 92 g. of the brown-colored liquid product was separated from the water. Decomposition resulted when an attempt was made to distill this product under reduced pressure. The *2,4-dinitrophenylhydrazone* derivative melted at 160–161° after recrystallization from methanol.

4,5-Dimethyl-2-carbamylmethylmercaptothiazole. A solution consisting of 83.5 g. (0.5 mole) of IX and 46.8 g. (0.5 mole) of chloroacetamide in 300 ml. of ethanol was agitated and heated under reflux for 5 hours. After filtering, alcohol was eliminated from the filtrate by evaporation. The crude product, 73 g., was recovered as buff-colored crystals, m.p. 99–108°. This compound was purified by recrystallization from ethanol.

3-o-Toluidinomethyl-4,5-dimethyl-2-thiono-4-thiazoline. To a solution of 72.5 g. (0.5 mole) of I and 20 g. (0.5 mole) of sodium hydroxide in 250 ml. of water was added, with agitation, 41 g. (0.5 mole) of 37% formaldehyde at 10°. This solution was cooled to 5–10° and 71.8 g. (0.5 mole) of *o*-toluidine hydrochloride was added with stirring. The precipitate which first formed was gummy but crystallization took place after agitating for 2 hours. Water was decanted from the reaction mixture, the solid product was dissolved in ethanol and after concentration of this solution, 119 g. of the white crystalline product, m.p. 103–105°, was obtained. As recrystallization resulted in decomposition, with the recovery of I, purification was effected by repeated extraction with ether.

4,5-Dimethyl-2-benzoylmercaptothiazole. To a suspension of 33.4 g. (0.2 mole) of IX in 300 ml. of benzene was added 28 g. (0.2 mole) of benzoyl chloride. The solution which formed was heated under reflux for 1 hour. Sodium chloride was removed and the filtrate was concentrated; yield, 49 g. of solid. Purification was effected by recrystallization from hexane.

Phthaloyl bis-(4,5-dimethylthiazole-2-sulfide). To a solution of 72.5 g. (0.5 mole) of I in 200 ml. of 10% aqueous sodium hydroxide was added, with agitation, 51 g. (0.25 mole) of phthalyl chloride at 30–35°. The precipitate which first formed was gummy but crystallized upon continued stirring; yield, 91 g. of crude material, m.p. 98–103°. Purification was effected by crystallization from ethanol.

4,5-Dimethyl-2-(2-furoyl)mercaptothiazole. To a suspension of 41.8 g. (0.25 mole) of IX in 300 ml. of benzene there was slowly added 32.7 g. (0.25 mole) of furoyl chloride. The reaction mixture was heated at 65–70° for 1 hour. After cooling to room temperature, sodium chloride was removed and the filtrate was concentrated; yield 56 g. of solid. Purification was effected by recrystallization from ether.

N-Diamyl-4,5-dimethyl-2-thiazolesulfenamide. A mixture of 145 g. (1 mole) of I, 157 g. (1 mole) of the diamylamine (mixed isomers), and 600 ml. of water was agitated while slowly adding 1,320 ml. of 8.5% aqueous sodium hypochlorite (1.5 mole) at 30–40°. After stirring for 1 hour, the brown liquid was separated from water to give 210 g. of crude product.

2-(o-Nitrophenyldithio)-4,5-dimethylthiazole. Forty-eight grams (0.25 mole) of *o*-nitrobenzenesulfenyl chloride was dissolved in 450 ml. of methanol and was added, with agitation, to a solution of 36.3 g. (0.25 mole) of I in 400 ml. of 2.5% aqueous sodium hydroxide

at 25–30°. The product, which first formed as a brown liquid, crystallized after stirring for 16 hours; yield 66 g., m. p. 80–83°. This compound was purified by recrystallization from ether.

6-Nitrobenzothiazole-4,5-dimethylthiazole-2,2'-monosulfide. Twenty-nine grams (0.2 mole) of I was dissolved in a solution of 8.5 g. (0.21 mole) of sodium hydroxide, 10 ml. of water, and 400 ml. of methanol. To this solution was added 43 g. (0.2 mole) of 2-chloro-6-nitrobenzothiazole and the mixture was heated under reflux for 45 minutes. A yellow, crystalline material was formed, yield, 50 g. of crude product, m.p. 118–120°. Purification was effected by crystallization from ether and ethanol.

4,5-Dimethylthiazole-2-sulfonic acid. Seventy-eight grams (0.85 mole) of nitrogen tetroxide vapor was passed into an agitated solution of 72.5 g. (0.5 mole) of I in 500 ml. of chloroform at 0–5°. The mixture was stirred for 45 minutes and was allowed to come to room temperature. The crude product (77 g., m.p. 260–263°) was obtained by filtration and by evaporation of the chloroform filtrate. Purification was effected by recrystallization from ethanol.

2,2'-Dithiobis-(4,5-dimethylthiazole) (6). A fine suspension of 72.5 g. (0.5 mole) of I in 250 ml. of water was prepared. To this agitated slurry was added 138 ml. (0.55 mole) of a 30% aqueous solution of ammonium persulfate in 30 minutes at 25–30°. Filtration yielded 66 g. of a buff-colored crystalline material, m.p. 46–48°, which was purified by recrystallization from hexane.

4,5-Dimethylthiazole. One hundred and six grams (0.8 mole) of I and 480 g. of 37% hydrochloric acid were agitated and while heating at 65–70°, 272 g. (2.4 moles) of hydrogen peroxide was added. After heating the mixture to 80° for 15 minutes, it was cooled to room temperature and 200 g. of barium chloride in 600 ml. of water was added. The precipitated barium sulfate was removed and the filtrate was concentrated under reduced pressure to about one-tenth of the original volume. The filtrate was neutralized with sodium hydroxide and the crude liquid product which separated was extracted with ether. After removing the ether there was obtained 57 g.

Lead salt. To an agitated solution of 72.5 g. (0.5 mole) of I, 20 g. (0.5 mole) of sodium hydroxide, and 1,200 ml. of water was added 82.8 g. (0.25 mole) of lead nitrate dissolved in 500 ml. of water. The yellow precipitate was recovered by filtration; yield 120 g.

Magnesium salt. To a solution of 72.5 g. (0.5 mole) of I in 200 ml. of 10% aqueous sodium hydroxide there was added, with agitation, a solution of 61.7 g. (0.25 mole) of magnesium sulfate in 600 ml. of water. The white precipitate amounted to 68 g.

Zinc salt. To a solution of 72.5 g. (0.5 mole) of I in 200 ml. of 10% aqueous sodium hydroxide there was added, with agitation, a solution of 34 g. (0.25 mole) of zinc chloride in 900 ml. of water; white precipitate, yield 84 g.

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SUMMARY

Methods for the synthesis and purification of twenty-three derivatives of 4,5-dimethyl-2-mercaptothiazole have been described. The sodium salt was reacted with acid chlorides and with halogenated members of the following classes of organic compounds: hydrocarbons, ketones, amides, and alkylamines. Heavy metal and alkaline earth salts were formed from water-soluble salts of the corresponding metals. 4,5-Dimethyl-2-mercaptothiazole reacted with formaldehyde to form a hydroxymethyl derivative which was further condensed with amines to form aminomethyl derivatives. The reaction with β-propiolactone

produced a thiazolyl substituted β-mercaptopropionic acid, and with acrylonitrile, a cyanoethyl derivative. Oxidation with nitrogen tetroxide, under mild conditions, gave the sulfonic acid.

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[Contribution from the Sterling Chemistry Laboratory, Yale University]

THE PREPARATION AND ABSORPTION SPECTRA OF α-(4-PYRIMIDYL)-ω-PHENYLPOLYENES

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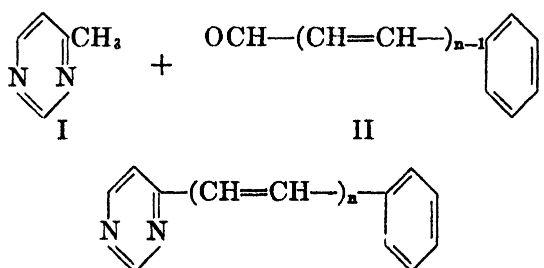
Previous work on polyenes having terminal, uncharged, aromatic groups has been restricted to the classical studies of Kuhn and Winterstein (1) on the diphenylpolyenes and the more recent studies of Compton and Bergmann (2) on the α-(α-quinolyl)-ω-phenylpolyenes. The present paper deals with an extension of such studies to a series of heterocyclic polyenes which differ from the diphenylpolyenes only in the replacement of one terminal phenyl group by the 4-pyrimidyl nucleus.

The first member of the α-(4-pyrimidyl)-ω-phenylpolyene series, (III, n = 1) is the only one which has previously been described. Its preparation was first accomplished by Gabriel and Colman (3) through the condensation of 4-methyl-



III

pyrimidine (I) with benzaldehyde (II, n = 1). The phenylpolyenealdehydes necessary for an extension of this series are available in reasonable yields through the method described by Schmitt (4). It consists in the condensation of a phenylpolyenealdehyde, such as cinnamaldehyde (IV), with crotonaldehyde (V), in the presence of piperidine acetate. Two aldehydes are the principal products of this reaction, 7-phenylheptatrienal (VI) and 11-phenylundecapentaenal (VII), of

$$\underset{\text{IV}}{C_6H_5CH{=}CHCHO} + \underset{\text{V}}{CH_3CH{=}CHCHO} \rightarrow$$

$$\underset{\text{VI}}{C_6H_5CH{=}CHCH{=}CHCH{=}CHCHO} +$$

$$\underset{\text{VII}}{C_6H_5CH{=}CHCH{=}CHCH{=}CHCH{=}CHCH{=}CHCHO}$$

which the latter is more readily isolated because of its lower solubility. In order to prepare the trienal (VI) without the simultaneous formation of substantial quantities of the pentaenal (VII) it has now been found of advantage to work in higher dilutions and to add the crotonaldehyde (V) dissolved in ethanol over a

period of seven days to a well-stirred alcoholic solution of cinnamaldehyde (IV). The condensation of the aldehydes with 4-methylpyrimidine was carried out by heating the reagents with zinc chloride at 120° for an extended period of time. The resulting zinc compounds were then decomposed by treatment with hydrochloric acid, and the free bases were liberated by addition of ammonia. A large excess of 4-methylpyrimidine was used with the higher aldehydes in order to effect their solution.

As shown in Table I, the colors of the pyrimidylphenylpolyenes show a gradation similar to that of the diphenylpolyenes. As in the case of the latter, the first member of the heterocyclic series showing definite coloration is the triene. The higher vinylogs of the heterocyclic series are, however, more deeply colored than the corresponding members of the diphenyl series. On the basis of visual evidence it appears therefore, that the chromophoric value of the 4-pyrimidyl group lies between that of a phenyl and a styryl group.

TABLE I

COMPARISON OF DIPHENYL- AND α-PYRIMIDYL-ω-PHENYLPOLYENES

n	C_6H_5-(CH=CH—)$_n$$C_6H_5$		$C_4H_3N_2$-(CH=CH—)$_n$$C_6H_5$	
	M.p, °C.	Color	M.p., °C.	Color
1	124	colorless	72	colorless
2	153	colorless	101	colorless
3	200	light-yellow	155	light-yellow
4	232	golden-yellow	194	golden
5	253	orange	218	orange-red
6	267	orange-red	239	red
7	279	bronze-red	—	dark red

A comparison of the absorption spectra maxima of the members of the two series indicates a similar relationship. Table II records the wave lengths of the absorption maxima of both series, which were measured in a chloroform solution, using a Beckman spectrophotomometer. Figure 1 shows the spectra of the members of the heterocyclic series. Like those of the diphenyl series, they show the typical increase of absorption intensity and curve character with the lengthening of the exocyclic chain. The fact that the heterocyclic polyenes exhibit less curve character than the diphenylpolyenes may be attributed to the presence of the nitrogen atoms which tend to stabilize one or more of the polar resonance forms. An increase in the contribution of polar resonance forms is usually associated with a loss of curve character, as is well shown by a comparison of the absorption spectra of cyanine dyes with those of diphenylpolyenes (6).

From a consideration of the electronic oscillation concept, Lewis and Calvin (5) have formulated the equation λ^2=kn, which relates λ, the wavelength of the absorption maximum, to n, the number of double bonds in the exocyclic chain. The data for the diphenylpolyene series are in excellent agreement with this relationship, and the data for the α-(α-quinolyl)-ω-phenylpolyene series (2) also

follows it closely. As shown by Figure 2, there is an increasing deviation from this relationship in the case of the α-(4-pyrimidyl)-ω-phenylpolyenes as the length of the exocyclic polyene chain is increased. This divergence indicates that

TABLE II

ABSORPTION MAXIMA IN CHLOROFORM AT 25°C.

COMPOUND	MAX. (mμ)		
	(a)	(b)	(c)
Diphenylethylene	299	310	—
Diphenylbutadiene	319	333	350
Diphenylhexatriene	342	357	377
Diphenyloctatetraene	361	379	401.5
Diphenyldecapentaene	379	399	424
Diphenyldodecahexaene	396.5	417.5	444.5
Diphenyltetradecaheptaene	411	434	462
Pyrimidylphenylethylene	—	316	—
Pyrimidylphenylbutadiene	—	344	—
Pyrimidylphenylhexatriene	—	370.5	—
Pyrimidylphenyloctatetraene	—	393.5	—
Pyrimidylphenyldecapentaene	—	414.5	—
Pyrimidylphenyldodecahexaene	—	432	—
Pyrimidylphenyltetradecaheptaene	—	447	471

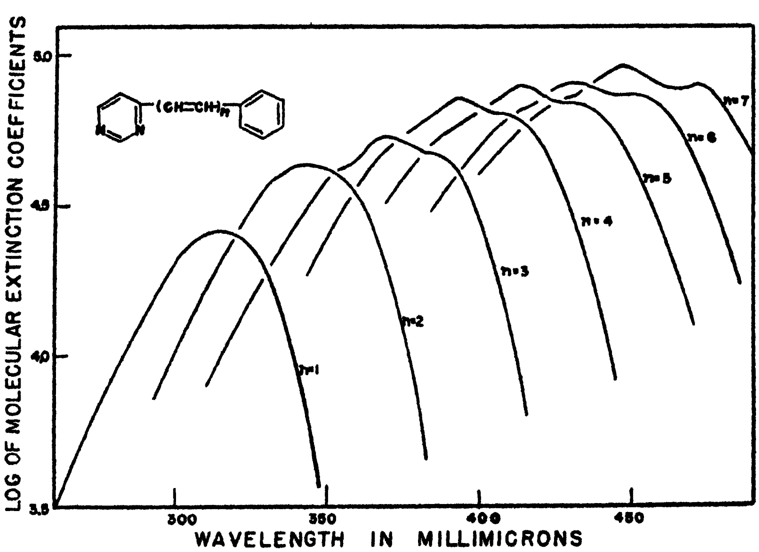


FIGURE 1. ABSORPTION CURVES OF α-(4-PYRIMIDYL)-ω-PHENYLPOLYENES IN CHLOROFORM AT 25°

the absorption maxima of the pyrimidyl-phenylpolyene series converge more rapidly than those of the diphenyl or the quinolyl-phenyl series. According to Brooker (6) rapid convergence of absorption maxima in a vinylogous series can be attributed to a considerable difference in the energies of the extreme resonance

structures involved, and to an increase in this difference as the chain is lengthened. Figure 2, therefore, indicates that the structures of the pyrimidyl-phenylpolyenes either differ somewhat more in energy, or show larger increases in energy difference with increasing chain lengths, than do the structures of the diphenylpolyenes or the quinolyl-phenylpolyenes.

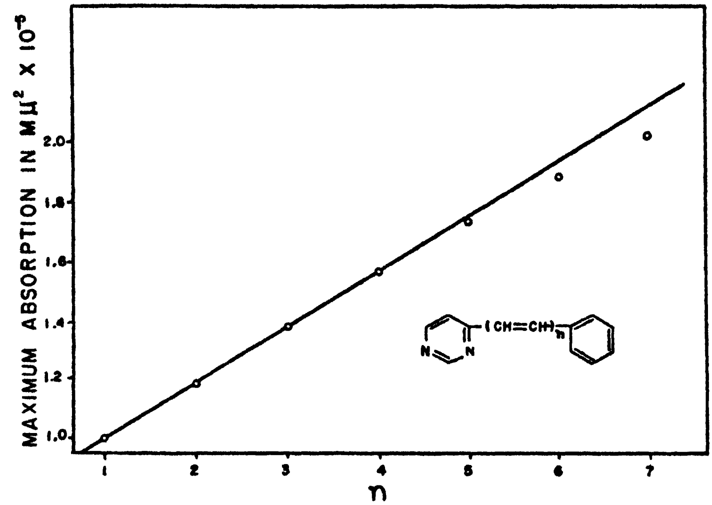


FIGURE 2. PLOT OF THE SQUARE OF THE WAVE LENGTH AGAINST THE NUMBER OF EXOCYCLIC DOUBLE BONDS

EXPERIMENTAL

All melting points are corrected.

7-Phenylheptatrien-2,4,6-al (VI). A mixture of 25 g. of piperidine, 25 g. of glacial acetic acid, and 132 g. (one mole) of freshly distilled cinnamaldehyde was dissolved in 600 cc. of 65% ethanol contained in a 2-liter, three-neck flask. The flask was equipped with a stirrer, a CO_2-inlet tube, and a one-liter dropping-funnel. The latter contained a solution of 35 g. (0.5 mole) of freshly distilled crotonaldehyde in 400 cc. of 65% ethanol under an atmosphere of CO_2. Through a capillary tube, attached to the dropping-funnel, the crotonaldehyde was added slowly over a period of a week to the solution containing the cinnamaldehyde. During the addition, the reaction mixture was stirred continuously and kept under an atmosphere of CO_2. The color of the solution slowly turned deep red, and crystals began to form after about one-half of the crotonaldehyde had been added.

After seven days the crystalline precipitate was collected and washed well with cold 70% ethanol. The mother liquor was kept under CO_2 for a week when a second crop of precipitate was obtained. The weight of the combined fractions was 49.5 g. The low melting point of the product, 108–112°, at once indicated that the material consisted chiefly of the *trienal*. The condensation product was then refluxed with one liter of 95% ethanol, and the solution filtered while still hot. There remained undissolved 6.4 g. of material, m.p. 173–178°, which consisted mainly of the *pentaenal* (VII).

The crude trienal obtained by cooling the filtrate was purified by three successive recrystallizations from ethanol containing small amounts of activated charcoal. The final product was obtained in form of nice yellow leaves; m.p. 116°. Yield, 32.6 g., or 35.5%.

1-(4-Pyrimidyl)-2-phenylethylene (III, n = 1). This compound was prepared by the procedure of Gabriel and Colman (3) with slight modifications. It melted at 71.5–72°.

1-(4-Pyrimidyl)-4-phenylbutadiene-1,3 (III, n = 2). A mixture of 4 g. (0.043 mole) of

freshly distilled 4-methylpyrimidine, 8 g. (0.061 mole) of freshly distilled cinnamaldehyde, and 0.5 g. of zinc chloride was heated for 10 hours in an oil-bath at 120° in a test tube fitted with a stopper containing a capillary. The mixture was then cooled, extracted with ether, and the ether extract washed with dilute hydrochloric acid. Upon addition of ammonia to the acid solution, a curdy, yellow product was precipitated, which after four recrystallizations from ethanol, including three treatments with Norit, gave 0.7 g. (8%) of a colorless, crystalline material, m.p. 100–101°.

Anal. Calc'd for $C_{14}H_{12}N_2$: C, 80.7; H, 5.8.
Found: C, 80.5; H, 5.9.

1-(4-Pyrimidyl) 6-phenylhexatriene-1,3,5 (III, n = 3). A mixture of 2 g. (0.021 mole) of freshly distilled 4-methylpyrimidine, 5 g of pentadienal, and 0.2 g. of zinc chloride was treated as described above. There was eventually obtained 0.08 g. (1.6%) of bright yellow needles, m.p. 154.8–155.3°. The product was soluble in ethanol, ether and chloroform, but only slightly soluble in dilute hydrochloric acid.

Anal. Calc'd for $C_{16}H_{14}N_2$: C, 82.0; H, 6.0.
Found: C, 81.8; C, 6.2.

1-(4-Pyrimidyl)-8-phenyloctatetraene-1,3,5,7 (III, n = 4). A mixture of 1 g. (0.005 mole) of 7-phenylheptatrienal, 3 g. (0.031 mole) of freshly distilled 4-methylpyrimidine, and 0.4 g. of zinc chloride was heated for eight hours at 125° as described above. After cooling the reaction product was filtered and washed with ethanol. This zinc compound was then digested with dilute hydrochloric acid for one hour, and the insoluble material was transferred to a thimble in a Soxhlet apparatus. The crude octatetraene hydrochloride was then extracted for eight hours with ethanol, and the resulting extract was made basic with ammonia. Upon dilution with water the octatetraene precipitated as an amorphous, yellow product, which after three recrystallizations from a mixture of toluene and ethanol gave 0.19 g. (21%) of bright golden crystals, m.p. 193–194°. The product is only slightly soluble in ethanol, but soluble in toluene and chloroform.

Anal. Calc'd for $C_{18}H_{16}N_2$: C, 83.0; H, 6.2.
Found: C, 82.9; H, 5.9.

1-(4-Pyrimidyl)-10-phenyldecapentaene-1,3,5,7,9 (III, n = 5). This compound was prepared from 4-methylpyrimidine and 9-phenylnonatetraenal (4) by a method analogous to the one described above, giving an orange-red, crystalline material; m.p. 217–218°, yield 1.25%. It is somewhat less soluble in all solvents tested than the preceding compound.

Anal. Calc'd for $C_{20}H_{18}N_2$: C, 83.9; H, 6.3.
Found: C, 83.5; H, 6.6.

1-(4-Pyrimidyl)-12-phenyldodecahexaene-1,3,5,7,9,11 (III, n = 6). This compound was prepared from 4-methylpyrimidine and 11-phenylundecapentaenal (4) by the procedure described above. Yield, 3.8%; fine, red crystals, m.p. 238–240°. The hexaene is practically insoluble in ethanol, moderately soluble in toluene and chloroform.

Anal. Calc'd for $C_{22}H_{20}N_2$: C, 84.6; H, 6.5.
Found: C, 84.2; H, 6.6.

1-(4-Pyrimidyl)-14-phenyltetradecaheptaene-1,3,5,7,9,11,13 (III, n = 7). This compound was prepared as described above from 4-methylpyrimidine and 13-phenyltridecahexaenal (4). Its great insolubility made purification exceedingly difficult, and it has not yet been possible to obtain an ash-free product. The crude product was a dark red, microcrystalline powder which upon heating began to decompose above 250°.

SUMMARY

A series of α-(4-pyrimidyl)-ω-phenylpolyenes has been prepared, and their absorption spectra have been measured and compared with those of the diphenylpolyene series.

NEW HAVEN, CONN.

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[Contribution from the Department of Industrial Chemistry, Faculty of Engineering, Kyôto University]

SYNTHESIS OF NEW HOMOLOGS OF HEXESTROL

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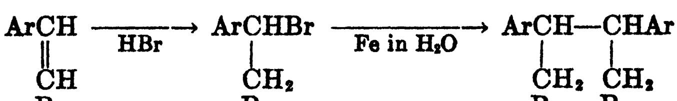
In a previous paper (1) we have described an effective method for the preparation of hexestrol and its homologs involving the dehalogenation condensation of *p*-(α-halogenoalkyl)anisoles with iron powder in a water suspension. In this procedure, not only are the reagents, *i.e.* iron and water, easily obtainable, but also the operation is simple and does not require the use of anhydrous conditions while all of the other published methods do. According to Quelet (2), since α-halogenoalkylanisoles are relatively unstable in the absence of moisture, they easily decompose, when dry, with the elimination of hydrogen halide. Our method has, therefore, an advantage also in this point.

We have now found that the use of reduced iron instead of the ordinary iron powder gives better results in this dehalogenation.

Kharasch and Kleiman (3) have pointed out the accelerating action of ferric, nickelous, or especially cobaltous chloride in a similar condensation employing a Grignard reagent in anhydrous ether. Recently Wilds and McCormack (4) have made an extensive investigation of the condensation catalyzed by cobaltous chloride and ascribe the catalytic action of the chloride to finely divided cobalt powder formed in the reaction. In connection with this view, further investigations on the syntheses in aqueous and non-aqueous mediums with iron, nickel or cobalt prepared under different reduction conditions are now under way in colaboration with an inorganic laboratory of our Department.

The present paper comprises the syntheses of 2,3-bis-(*p*-hydroxy-*m*-tolyl)butane, 3,4-bis-(*m*,*p*-dihydroxyphenyl)hexane, 3,4-bis-(*p*-hydroxy-*o*-tolyl)hexane, 4,5-bis-(*p*-hydroxyphenyl)octane, 2,7-dimethyl-4,5-bis-(*p*-hydroxyphenyl)octane, 5,6-bis-(*p*-hydroxyphenyl)decane, and 6,7-bis-(*p*-hydroxyphenyl)dodecane. The reactions used in the preparations are, in general, as follows.



R = Alkyl; Ar = Aryl

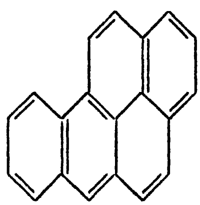
Although the synthesis of the diphenylhexatriacontane derivative (R = $C_{16}H_{33}$) was not successful, the reaction seems to be widely applicable to the preparation of derivatives of the α,α'-dialkylbibenzyl type with the exception of higher members.

The new compound, 2,3-bis-(*p*-hydroxy-*m*-tolyl)butane, now synthesized, corresponds to 2,3-bis-(*p*-hydroxy-*m*-tolyl)-2-butene, a new estrogen found by us (5). Since the pairs, hexestrol and diethylstilbestrol as well as 2,3-bis-(*p*-hydroxy-*o*-tolyl)butane (6) and 2,3-bis-(*p*-hydroxy-*o*-tolyl)-2-butene (5, 7) have an ac-

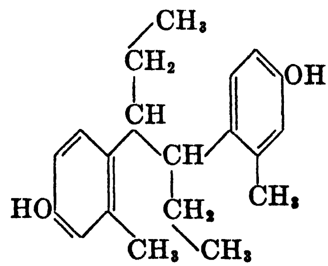
tivity of the same order, we anticipate its estrogenity although the *in vivo* test is not completed.

For the sake of comparison with 3,4-bis-(*p*-hydroxy-*m*-tolyl)hexane, an estrogen of high activity and low toxicity found by Niederl, Siconolfi, Bloom, and Van Meter (8), a new isomer, 3,4-bis-(*p*-hydroxy-*o*-tolyl)hexane, was prepared.

In the study of estrogenic substances having a 1,3-diarylpropane structure, Stuart, Shukis, Tallman, McCann, and Treves (9) have noted a structural resemblance of highly active benzestrol with the carcinogens, 9,10-dimethyl-1,2-benzanthracene and cholanthrene. It is interesting to prepare other phenolic substances with an open skeleton of a carcinogenic hydrocarbon. 3,4-Bis-(*p*-hydroxy-*o*-tolyl)hexane mentioned above is a symmetrical open model of 3,4-benzopyrene.



3, 4-Benzopyrene



3, 4-Bis-(*p*-hydroxy-*o*-tolyl)hexane

3,4-Bis-(*m*,*p*-dihydroxyphenyl)hexane was prepared already by Baker (10) in another way. This compound is an isomer of nordihydroguaiaretic acid (11) and activity also as an antioxidant of fatty oils is expected.

An attempt to synthesize genuine nordihydroguaiaretic acid from safrole hydrobromide (a compound with a bromine atom attached to the β-position from the atomatic ring) by means of this condensation reaction resulted in failure. Styrene dibromide, on treatment with iron in water, also did not give any condensation product other than styrene and styrene dimer. Funakubo and Ootuka (12) described a similar dehalogenation of α,β-dihalogeno-α-phenylpropane.

The biological testing of these compounds is being carried out in the laboratory of Prof. Kinosita of Osaka University Medical School. The pharmacological results will be published elsewhere.

EXPERIMENTAL

Improved preparation of 3,4-di-p-anisylhexane (1). A solution of 40 g. of anethole (synthesized from *p*-bromoanisole and allyl bromide) in 200 cc. of toluene was saturated with dry hydrogen bromide under cooling with an ice-salt mixture. After washing with ice-cooled water the toluene solution was added dropwise with stirring to a suspension of 24 g. of reduced iron [ferrum reductum, P.J.V. (Fifth Pharmacopoeia of Japan) grade] in 240 cc. of hot water maintained at 80–98°. The addition required about fifteen minutes, during which the toluene was distilled from the reaction vessel. In the course of this the toluene solution contained in a dropping-funnel attached to the reaction flask was added directly with several pieces of crushed ice in order to prevent the decomposition of the halogeno compound

and to supply the water driven off with the toluene. The reaction mixture then was heated under a reflux condenser for an additional three hours at 95–98° and allowed to cool. The product was extracted with ether and the ether solution was washed with water, dried, and the solvent was evaporated. Recrystallization of the residue from methanol-ligroin afforded colorless plates, m.p. and mixed m.p. with *meso*-3,4-di-*p*-anisylhexane 144°; yield, 8.1 g. (20%).

The mother liquor was distilled *in vacuo* and 9 g. of a fraction b.p. 70–115° at 23 mm. and 17 g. of a fraction b.p. 180–200° at 6 mm. were obtained. The latter fraction, which seemed to consist of *racemic* dianisylhexane and possibly of anethole dimer etc., did not give any crystalline product when treated with methanol-ligroin. The lower-boiling fraction contained, according to the analysis by the method of McIlhiney (13), 85% of anethole. The purity of the starting anethole was, according to the same analysis, 99.5%. Allowing for recovered anethole the yield of hexestrol dimethyl ether was 25%.

When anethole hydrochloride was used instead of the hydrobromide in the present condensation, lower yields (14–15%, without considering the recovered material) were obtained.

*2,3-Bis-(p-hydroxy-m-tolyl)butane.** A mixture of 10 g. of *p*-vinyl-*o*-methylanisole prepared by the method of Quelet (14), and 50 cc. of ligroin was saturated with hydrogen chloride at −8 to −10° and was treated with 5 g. of reduced iron powder and 60 cc. of water at about 100° for four hours as above. There was obtained 6 g. of a fraction b.p. 180–193° at 6 mm. together with 3 g. of a lower-boiling fraction which contained the starting material. Crystallization from methanol-ligroin afforded 1.5 g. of colorless crystalline *meso-2,3-bis-(p-methoxy-m-tolyl)butane,** m.p. 124–125°.

Anal. Calc'd for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78.
Found: C, 80.93; H, 8.40.

Demethylation with a Grignard reagent or with hydriodic acid in glacial acetic acid and recrystallization from benzene gave *meso-2-3-bis-(p-hydroxy-m-tolyl)butane,** m.p. 174–174.5°, in large colorless crystals which changed soon to a white powder. Due perhaps to this property the analysis did not give satisfactory values. Bretschneider, de Jonge-Bretschneider, and Ajtai (6) reported a similar case.

The *diacetate** prepared with acetic anhydride and pyridine melted at 145–145.5° after recrystallizations from alcohol.

Anal. Calc'd for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39.
Found: C, 74.80; H, 7.42.

3,4-Bis-(m,p-dihydroxyphenyl)hexane. A solution of 50 g. of isosafrole with a purity of 99.3% in 100 cc. of ligroin was saturated with hydrogen bromide and treated with 20 g. of iron powder in 200 cc. of water as above. The reaction product separated during the operation as white crystals. The reaction mixture was extracted with benzene and 12 g. of crystals was obtained. From the mother liquor there was obtained on distillation *in vacuo* 1 g. of a fraction b.p. 60–100° at 35–40 mm., 9 g. of a fraction b.p. 120–130° at 35–40 mm., and 13 g. of a fraction b.p. 210° at 3 mm. On analyses according to McIlhiney (13), the lower-boiling fractions contained 43.0 and 91.2%, respectively, of isosafrole. The last fraction gave on recrystallization from benzene-alcohol an additional 4 g. of the above mentioned crystals. Recrystallized from benzene-alcohol the combined crystals gave 12 g. of *meso-3,4-bis-(m,p-methylenedioxyphenyl)hexane,** m.p. 174–175°.

Anal. Calc'd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79.
Found: C, 73.65; H, 6.74.

A mixture of 10 g. of 3,4-bis-(*m,p*-methylenedioxyphenyl)hexane, 45 g. of toluene, and 42 g. of phosphorus pentachloride was refluxed for three hours and the resulting 3,4-bis-(*m,p*-dichloromethylenedioxyphenyl)hexane* was decomposed with ice and a saturated sodium carbonate solution. From the toluene layer, after washing with water, drying, and evaporation, 6 g. of *3,4-bis-(m,p-carbonyldioxyphenyl)hexane** was obtained, which after recrystallization from toluene melted at 186–187°.

* Indicates a new compound.

Anal. Calc'd for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12.
Found: C, 67.32; H, 5.05.

A mixture of 6 g. of the carbonyldioxy compound, 320 g. of methanol, and 100 cc. of conc'd hydrochloric acid was heated at 78° in an atmosphere of carbon dioxide for 2½ hours and evaporated *in vacuo*. When about two-thirds of the solvent was distilled off, the phenolic substance deposited in white fine crystals, which were filtered and dried on porous plate. Yield, 5 g. After recrystallization from 50% acetic acid the compound melted with decomposition at 230–235°. This melting point coincides with the one reported by Baker (10).

On acetylation and recrystallization from alcohol, the phenol gave *the tetraacetate,** m.p. 167–167.5°. The same tetraacetate was prepared also directly from the methylenedioxy compound by the cleavage of the methylenedioxy ring with acetic anhydride. When 2 g. of the methylenedioxy compound and 6.5 g. of acetic anhydride were heated at 200° for fifteen hours in a sealed tube considerable carbonization took place, but 0.3 g. of the impure tetraacetate and 1 g. of unchanged material were obtained.

Anal. Calc'd for $C_{26}H_{30}O_8$: C, 66.37; H, 6.43.
Found: C, 66.08; H, 6.23.

Variations in the condensation procedure. In order to determine the best conditions for this dehalogenation reaction, we carried out the following three experiments employing isosafrole. In each case, 100 g. of isosafrole in 150 g. of toluene was saturated with hydrogen bromide at $-10 \pm 3°$ and condensed by means of 40 g. of reduced iron powder in 400 cc. of water.

(a) A mixture of iron powder and water was heated to 100° and the hydrobromide solution was added slowly at such a rate that toluene distilled off completely from the reaction vessel. The addition required about one hour. There was obtained 35 g. of a lower-boiling fraction and 45 g. of a condensate fraction which gave 20 g. of the crude crystalline *meso* compound and a resinous residue.

(b) Into a mixture of iron powder and water heated to about 80–90° the hydrobromide solution was added in the course of twenty minutes regardless of the rate of distilling toluene. There was obtained 33 g. of a lower-boiling fraction and 53 g. of a condensate including 25 g. of the *meso* crystals.

(c) Iron powder, water, and the hydrobromide solution were mixed to an emulsion at room temperature and heated gradually until toluene was azeotropically distilled off. Twenty-five grams of a lower-boiling fraction and 50 g. of a condensate fraction were obtained. The latter gave 23 g. of the *meso* crystals.

Attempted synthesis of 2,5-bis-(m,p-methylenedioxyphenyl)hexane. Thirty grams of safrole hydrobromide, b.p. 130–140° at 8 mm., 15 g. of iron powder, and 150 cc. of water were heated to reflux under stirring for two hours, but only very small amount of a condensation product was obtained. Even when we used an active cobalt powder freshly reduced instead of iron, almost the same result was obtained.

*3,4-Bis-(p-hydroxy-o-tolyl)hexane.** *p*-Methoxy-*o*-methylpropiophenone was prepared from *m*-cresol methyl ether and propionyl chloride by the Friedel-Crafts reaction and reduced to the corresponding carbinol with sodium in isoamyl alcohol. The carbinol was dehydrated with potassium bisulfate to *o*-methylanethole. A solution of 10 g. of *o*-methylanethole in 60 cc. of ligroin or toluene was saturated with hydrogen bromide and treated with 7 g. of iron powder in 60 cc. of water as above. There was obtained 6 g. of a lower-boiling fraction and 3 g. of a condensation product which afforded on repeated recrystallizations from methanol large prisms of *meso-3,4-bis-(p-methoxy-o-tolyl)hexane,** m.p. 129–130°, yield, 0.6 g.

Anal. Calc'd for $C_{22}H_{30}O_2$: C, 80.93; H, 9.26.
Found: C, 81.04; H, 9.27.

Demethylation with hydriodic acid and glacial acetic acid and recrystallizations from benzene yielded *meso*-3,4-bis-(*p*-hydroxy-*o*-tolyl)hexane, m.p. 218–219°.

Anal. Calc'd for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78.
Found: C, 80.42; H, 8.45.

The *diacetate,** recrystallized from ligroin formed needles melting at 153°.

Anal. Calc'd for $C_{24}H_{30}O_4$: C, 75.36; H, 7.91.

Found: C, 75.17; H, 8.02.

4,5-Bis-(p-hydroxyphenyl)octane (octestrol). Starting from anisole and *n*-butyryl chloride the corresponding arylalkene was obtained. Ten grams of this olefin gave, besides 4 g. of a lower-boiling fraction, 3.5 g. of a condensate which gave on recrystallization from methanol 1 g. of *meso*-4,5-bis-(*p*-methoxyphenyl)octane, m.p. 121–122°.

Anal. Calc'd for $C_{22}H_{30}O_2$: C, 80.93; H, 9.26.

Found: C, 80.71; H, 9.00.

On demethylation and recrystallization from benzene long needles of *meso*-4,5-bis-(*p*-hydroxyphenyl)octane, m.p. 166–167°, were obtained.

Anal. Calc'd for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78.

Found: C, 80.27; H, 8.70.

The melting points of the hydroxy and the methoxy compounds coincide with those recorded by Dodds, Golberg, Grünfeld, Lawson, and Saffer (15).

The *diacetate,** crystallized from ligroin, m.p. 167.5–168.5°.

Anal. Calc'd for $C_{24}H_{30}O_4$: C, 75.36; H, 7.91.

Found: C, 75.32; H, 7.96.

*2,7-Dimethyl-4,5-bis-(p-hydroxyphenyl)octane.** Using 13 g. of the olefin derived from isovaleryl chloride as above, 3 g. of an oily reaction product and 7 g. of a lower-boiling fraction were obtained.

Since this oily mixture of *meso* and *racemic* compounds did not give any crystalline substance, it was demethylated as such and gave 0.5 g. of a hydroxyphenyl compound. On repeated recrystallizations from benzene, long colorless needles were obtained, which changed soon to white powder. The melting point was not sharp, 167–170°.

Anal. Calc'd for $C_{22}H_{30}O_2$: C, 80.93; H, 9.26.

Found: C, 80.59; H, 8.77.

The *diacetate** melted at 187–190°.

Anal. Calc'd for $C_{26}H_{34}O_4$: C, 76.06; H, 8.35.

Found: C, 75.84; H, 7.91.

*5,6-Bis-(p-hydroxyphenyl)decane (decestrol).** Twelve grams of the olefin derived from *n*-valeryl chloride afforded 2.5 g. of an oily condensation product in addition to 7 g. of a lower-boiling fraction. On demethylation, 1 g. of crystalline *meso*-5,6-bis-(*p*-hydroxyphenyl)decane was obtained in long needles, m.p. 170–171° from benzene.

Anal. Calc'd for $C_{22}H_{30}O_2$: C, 80.93; H, 9.26.

Found: C, 80.56; H, 9.04.

The *diacetate,** m.p. 128.5–129°.

Anal. Calc'd for $C_{26}H_{34}O_4$: C, 76.06; H, 8.35.

Found: C, 75.78; H, 7.99.

*6,7-Bis-(p-hydroxyphenyl)dodecane.** Twenty grams of the corresponding olefin from caproic acid gave 10 g. of a lower-boiling fraction and 6 g. of an oily product which on demethylation yielded 2 g. of a crystalline phenolic compound. Repeated recrystallizations from benzene yielded hair-like crystals, m.p. 145–146°.

Anal. Calc'd for $C_{24}H_{34}O_2$: C, 81.31; H, 9.66.

Found: C, 81.17; H, 9.39.

The *diacetate** formed fibrous brilliant crystals, m.p. 98–99°, from ligroin.

Anal. Calc'd for $C_{28}H_{38}O_4$: C, 76.67; H, 8.73.

Found: C, 76.19; H, 8.88.

Attempted synthesis of 18,19-bis-(p-hydroxyphenyl)hexatriacontane. Analytically pure *p*-methoxystearophenone, m.p. 78–79°, was reduced to the corresponding carbinol and dehydrated to the olefin, b.p. 170–180° at 0.015 mm. The toluene solution of this olefin was saturated with hydrogen bromide in the same manner. Treatment of the product with iron powder, however, failed to afford any distillable condensation product.

Reaction of styrene dibromide with iron. Twenty-five grams of styrene dibromide, 5.6 g.

of iron powder, and 64 cc. of water were heated to reflux under stirring for eight hours, and treated as usual. There was obtained 2.5 g. of a fraction, b.p. 50–57° at 20–30 mm. and 2.7 g. of the higher-boiling oily fraction, b.p. 110–120° at 5 mm. Bromination of the first fraction gave styrene dibromide, m.p. and mixed m.p. 72–73°. The higher-boiling fraction gave no crystalline substance and was negative in the Beilstein test. As it absorbed bromine, it was assumed to be a dimer of styrene. These results indicate the occurrence of an intramolecular dehalogenation (12) followed by polymerization.

SUMMARY

By the dehalogenation condensation of α-halogenoalkylanisoles with metallic iron powder in a water suspension. some homologs of hexestrol were prepared. This dehalogenation procedure seems to be applicable in general.

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PREPARATION AND PHYSICAL PROPERTIES OF CERTAIN DI-N-ALKYL ZINC COMPOUNDS[1,2]

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Di-*n*-alkyl zinc compounds were first prepared in 1853 by Frankland (1) by heating zinc and the alkyl iodide in a sealed tube. Since that time the preparation of these compounds has been studied by a number of investigators culminating in the procedure of Noller (2) with modifications by Soroos and Morgana (3). The reaction is that of the alkyl iodide (or a mixture of the iodide and bromide) with an alloy consisting of 90% zinc and 10% copper.

Although there is considerable information in the literature pertaining to the preparation and chemical properties of the lower molecular weight alkyl zinc compounds, there is a paucity of reliable data related to their physical properties. The present study was undertaken to obtain more extensive and more accurate physical data on di-*n*-propyl zinc, di-*n*-butyl zinc, di-*n*-pentyl zinc, di-*n*-hexyl zinc, and di-*n*-heptyl zinc. The latter two compounds have not been reported previously.

Of the various methods reported for the preparation of alkyl zinc compounds, the one developed by Noller appeared to be the most efficient and least expensive procedure for the preparation of the relatively large quantities of the compounds required. The halide used was usually the iodide but in some cases a mixture of the iodide and bromide was used. The zinc was in the form of an alloy with copper (Zn 91%, Cu 9%). All preparations were carried out under dry nitrogen or helium. Table I records the yields obtained along with the density and analysis of the alkyl zinc compounds. The compounds were analyzed by determining the amount of zinc oxide formed by slow air oxidation. The yields generally decreased with increase in molecular weight primarily because of increased difficulty of recovery by distillation.

The ease of decomposition of the di-*n*-alkyl zinc compounds did not permit a determination of their boiling points at atmospheric pressure. Atmospheric boiling points were obtained for each of the five di-*n*-alkyl zinc compounds by determining the boiling temperatures of each compound at reduced pressures and plotting $\log_{10}P$ vs $1/T$. The "best" representative straight line was drawn through the resulting points and extended to an ordinate corresponding to $\log_{10}760$ (Fig. 1). The value of $1/T$ thus obtained was used to determine the boiling point of the compound at 760 mm. The precision was $\pm 2°$. These boiling points are presented graphically in Fig. 2 along with data from the literature (2, 4–10).

[1] The research described in this paper was carried out at the Defense Research Laboratory of the University of Texas. This laboratory operates under contract NOrd-9195 between the University of Texas and the Bureau of Ordnance of the Navy Department.

[2] A portion of this paper was presented at the 115th meeting of the American Chemical Society, March 28–April 1, 1949, at San Francisco, California.

TABLE I
ZINC ALKYLS

COMPOUND	YIELD, %	DENSITY $\frac{20^\circ}{4^\circ}$	ANALYSIS Zn, %		
			Calc'd	Found	
Di-*n*-propyl zinc	67	1.080	43.8	43.9	43.9
Di-*n*-butyl zinc	71	1.034	36.5	36.3	36.2
Di-*n*-pentyl zinc	58	0.990	31.5	31.2	31.0
Di-*n*-hexyl zinc	51	.996	27.8	27.4	27.3
Di-*n*-heptyl zinc	41	.997	24.8	24.5	24.4

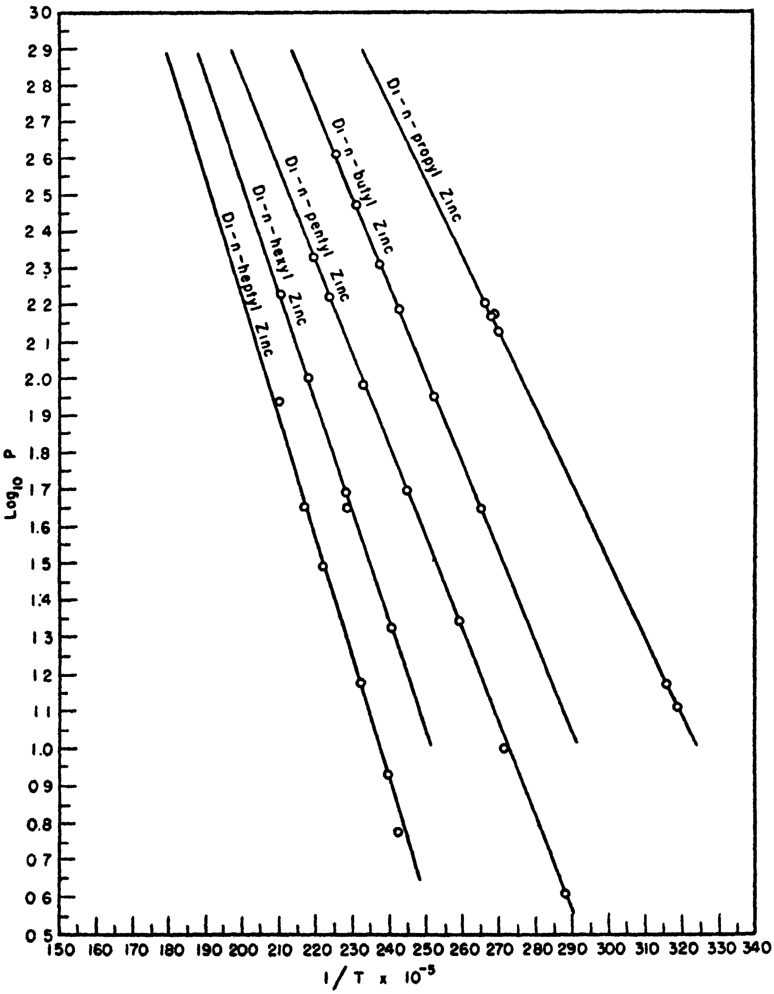

FIG. 1. DI-*n*-ALKYL ZINC COMPOUNDS. RECIPROCAL OF THE BOILING TEMPERATURE *vs.* LOG10 OF THE PRESSURE

An average value of the molar heat of vaporization for each of the di-n-alkyl zinc compounds (Fig. 3) was calculated using data obtained in the boiling point determinations. These data were substituted in the Clapeyron equation: $\ln(P_1/P_2) = (\Delta H_v/R) \times (T_2 - T_1/T_1T_2)$. Data from the literature (5, 7) are also

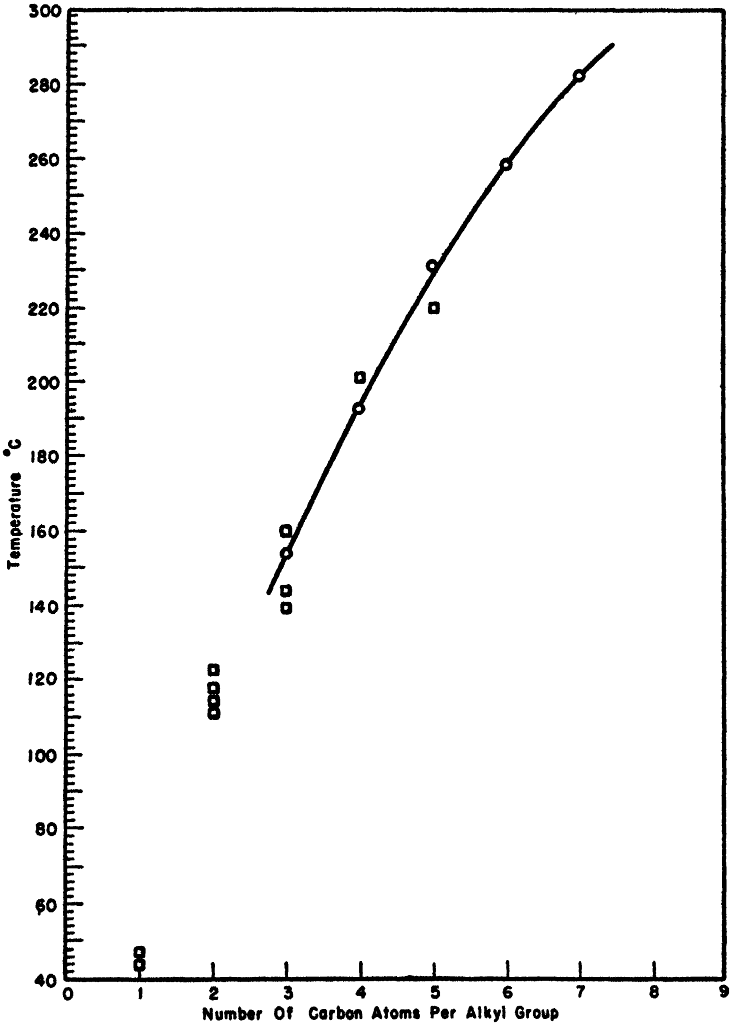

FIG. 2. BOILING POINTS AT 760 MM. PRESSURE OF DI-n-ALKYL ZINC COMPOUNDS. ○, DEFENSE RESEARCH LABORATORY DATA (CALCULATED). □, LITERATURE DATA (MOST POINTS CALCULATED)

given in Fig. 3. The constants were also calculated for the equation, $\log_{10}P = -A/T + B$, which describes the vapor pressure-boiling temperature curves. A value for Trouton's quotient (the normal entropy of vaporization) was calculated using the atmospheric boiling points and the average molar heats of vaporization

for each of the di-*n*-alkyl zinc compounds. All of the quotients are larger than the approximate value, 21, which is given in the literature for various liquids.

The foregoing thermodynamic constants are given in Table II.

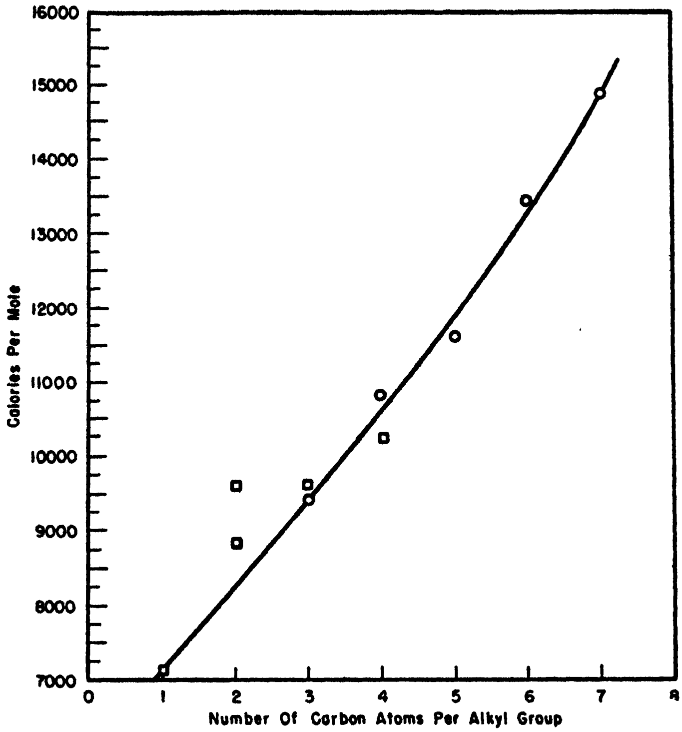

FIG. 3. MOLAR HEAT OF VAPORIZATION OF DI-*n*-ALKYL ZINC COMPOUNDS. ○, DEFENSE RESEARCH LABORATORY DATA (CALCULATED). □, LITERATURE DATA (CALCULATED)

TABLE II

THERMODYNAMIC CONSTANTS OF CERTAIN DI-*n*-ALKYL ZINC COMPOUNDS

COMPOUND	BOILING POINT[a] @ 760 MM, °C.	ΔH_v (cals.)	A	B	$\Delta H_v/T$
Di-*n*-propyl zinc..................	154	9433	2067	7.707	23.086
Di-*n*-butyl zinc..................	193	10828	2366	7.957	23.236
Di-*n*-pentyl zinc..................	231	11627	2543	7.925	23.064
Di-*n*-hexyl zinc..................	258	13434	2920	8.390	25.300
Di-*n*-heptyl zinc..................	282	14896	3296	8.754	26.840

[a] Calculated.

All of the di-*n*-alkyl zinc compounds prepared during this investigation are very sensitive to even traces of oxygen or moisture. On contact with either air or water there is a vigorous exothermal reaction resulting in the formation of various zinc and organic compounds.

Small droplets of di-*n*-propyl zinc were spontaneously flammable in air and in water at 25°. Di-*n*-butyl zinc burned when droplets came in contact with air while receivers were changed during distillation; however, the butyl compound did not inflame when sprayed into air from a hypodermic needle at room temperature. Considerable heat was evolved when the pentyl, hexyl, and heptyl derivatives came in contact with either air or water but they did not ignite.

When the compounds were stored in glass containers which were sealed to prevent access of air, there was no visible evidence of decomposition over a period of eight months. Some type of reaction seems to have taken place, however, because an alkyl compound which has been stored for several weeks or longer will decompose rapidly if the bottle is opened only momentarily. The nature of this decomposition differs from the normal oxidation; very little white zinc oxide is formed but instead a precipitate of black zinc is produced.

EXPERIMENTAL

PREPARATION OF THE DI-*n*-ALKYL ZINC COMPOUNDS

All of the di-*n*-alkyl zinc compounds were prepared in a Grignard type apparatus using a zinc (91%)-copper (9%) alloy and the desired *n*-alkyl iodide under an atmosphere of dry nitrogen (99.99%) or pure helium. The alloy was milled to give pieces approximately 3 × 10 mm. The alkyl iodides were obtained from Columbia Organic Chemical Company and were used without further purification because the small amount of iodine present seemed to be instrumental in initiating reaction.

Both isopropyl ether and *n*-butyl ether were especially dried and used as solvents. Isopropyl ether was used in the preparation of di-*n*-propyl and di-*n*-butyl zinc because its boiling point, while lower than the boiling points of both *n*-propyl iodide and *n*-butyl iodide, was high enough to initiate the reaction. The higher-boiling *n*-butyl ether was used in the preparation of the other three di-*n*-alkyl zinc compounds. The reactions were carried out at the reflux temperature of the ether used.

The tendency towards decomposition during the reaction phase seemed to increase with decreasing size of alkyl groups. A slight amount of fuming was observed during the preparation of the hexyl and heptyl derivatives. The fumes, however, were more dense during the preparation of the pentyl derivative, and a small layer of zinc oxide was deposited above the dark residual powder in the reaction flask. The butyl and propyl reaction mixtures were very sensitive to excessively rapid stirring and excessive heating, and considerable fuming and deposition of zinc oxide were observed. The sensitivities of the *n*-alkyl zinc compounds toward impurities in the nitrogen with resulting decomposition, also increased with decreasing size of the alkyl group.

After a four-hour reaction period (two hours for the addition of the iodide and two hours refluxing) the liquid contents of the reaction flask were then transferred by decantation to the distillation flask. This transfer was accomplished in a nitrogen-filled dry-box. The apparatus used for the distillation of the di-*n*-alkyl zinc compounds consisted of a flask, 180 mm. Vigreux column, 250 mm. condenser, vacuum receiver, and product bottle. The column was insulated with Eagle-Pitcher Company's "Eagle 66". The distillation step in the preparation of these compounds is the most important one and governs the yield obtained. Pressures between 1 and 10 mm. were used in these distillations. The yields obtained are given in Table I.

ANALYSIS

Quantitative determinations of zinc were made on the five di-*n*-alkyl zinc compounds which were prepared in this study. The fact that all the compounds are easily oxidized by

air to form zinc oxide was used as the basis for these analyses. In order to obtain a quantitative conversion of the zinc in the di-*n*-alkyl zinc compound to zinc oxide, the reaction rate was decreased by dissolving a known quantity of the di-*n*-alkyl zinc compound in *n*-pentane, and then permitting the solvent to evaporate slowly.

Small glass capsules were used to handle the di-*n*-alkyl zinc compounds. These capsules were formed by blowing bulbs of 8 mm. diameter from 5-mm. Pyrex glass tubing. The glass tubing was broken two inches above the bulb, and then the two inch neck was drawn into a constriction, yielding a capsule consisting of the bulb with an 1¼ inch neck that had a constricted opening of about 3 mm.

About 0.5 ml. of the compound was transferred quickly from the bottle to the previously weighed capsule by means of a hypodermic syringe. The capsule was then sealed, weighed and placed in a weighed crucible containing *n*-pentane. The capsule was broken at the junction of the bulb and neck. The *n*-pentane was allowed to evaporate in a desiccator which contained calcium chloride. The crucible containing the zinc oxide was heated for one hour in an oven at 100° before determining the amount of oxide formed. The analytical results are in Table I.

DENSITY

A determination of the density of each of the five di-*n*-alkyl zinc compounds was made at $\frac{20^\circ}{4^\circ}$. The determination was made on di-*n*-pentyl, di-*n*-hexyl, and di-*n*-heptyl zinc by using a vacuum-jacketed specific gravity bottle which was equipped with a ground glass stopper containing a capillary tube and a glass stopper cover. An AMINCO refrigerated constant temperature bath was used to obtain a constant temperature of 20°.

In order to reduce decomposition as much as possible, the di-*n*-alkyl zinc compounds and the pycnometer were cooled separately at 20° in the constant-temperature bath before the di-*n*-alkyl zinc was transferred to the pycnometer. When the bottle containing the di-*n*-alkyl zinc had been in the bath for one hour, the pycnometer was removed and dried thoroughly. As quickly as possible, the cover and stopper were removed, the bottle with the di-*n*-alkyl zinc compound was then taken out of the bath and opened. Five and two tenths ml. of the liquid was rapidly removed with a hypodermic syringe and ejected into the pycnometer. When the liquid level had risen a slight distance up the neck of the pycnometer, the glass stopper was replaced. All surplus liquid was forced out through the capillary tube in the stopper and was removed with a towel. All traces of zinc oxide were also wiped away, the glass cover replaced, and the pycnometer quickly weighed. The transference and weighing had to be accomplished as rapidly as possible to prevent the heat of decomposition from changing the temperature of the liquid.

The propyl and butyl derivatives were too reactive to allow their densities to be determined in the manner used for the higher molecular weight compounds. The densities of di-*n*-propyl and di-*n*-butyl zinc were determined by low temperature distillation of the compound into a calibrated dilatometer which was then sealed (11).[3]

At least two determinations of the density of each of the di-*n*-alkyl zinc compounds were made to obtain results which differed by less than one unit in the third decimal place (Table I).

BOILING POINTS AT REDUCED PRESSURES

The ease of decomposition of the di-*n*-alkyl zinc compounds did not permit a determination of their boiling points at atmospheric pressure. The boiling points at 760 mm. pressure were determined by obtaining the boiling points of each compound at a number of different pressures below atmospheric and from these data the desired points were calculated by extrapolation from a line obtained by plotting the reciprocal of the boiling temperature (in degrees Kelvin) at the reduced pressure against the $\log_{10}$ of the pressure. The line thus ob-

[3] These data were obtained by Elizabeth A. Mayer.

tained was linear over the limited range used and corresponded to the equation $\log_{10}P = -A/T + B$, where T represents the boiling temperature, P the pressure and A and B are constants.

The apparatus used for the determination of the boiling point-pressure data for these compounds consisted of a flask and a 180-mm. Vigreux column with the appropriate condenser and vacuum receiver. The column was insulated with Eagle-Pitcher Company's "Eagle 66". The vacuum was provided by a Cenco Hyvac vacuum pump operating through a Dry Ice-isobutyl alcohol cold trap and regulated by a needle valve. The pressure was measured by a differential manometer. At each pressure equilibrium was established and the temperature in the still head noted using a standardized thermometer; the appropriate stem corrections were made.

The data obtained are given in Table II and in Fig. 1.

SUMMARY

The following di-*n*-alkyl zinc compounds have been prepared and certain of their physical properties determined: Di-*n*-propyl zinc, di-*n*-butyl zinc, di-*n*-pentyl zinc, di-*n*-hexyl zinc, and di-*n*-heptyl zinc.

AUSTIN, TEXAS

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[EXPERIMENTAL BIOLOGY AND MEDICINE INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

CYCLITOL DERIVATIVES. I. DERIVATIVES OF *RAC.-EPI*-INOSOSE

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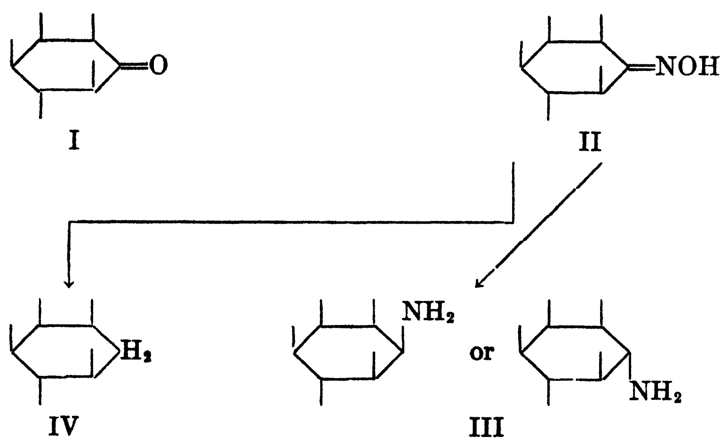
Received June 24, 1949

This is the first of a series of papers dealing with the synthesis of cyclitol derivatives.[1] It describes a number of nitrogen-containing compounds derived from *rac.-epi*-inosose (I).

The oxime (II) of *rac.-epi*-inosose could be obtained crystalline by adhering strictly to certain experimental conditions. Hydrogenation of II with platinum oxide in 70% methanol gave inosamine (III)[2] in a yield of 70%. When the hydrogenation was conducted in dilute acetic acid, a mixture consisting of *epi*-inositol and inosamine (III), was obtained in rather low yield; in dilute hydrochloric



acid only a desoxy-inositol (IV)[3] and very small amounts of *epi*-inositol (3) were formed. Catalytic hydrogenation of the semicarbazone of I gave a semicarbazide derivative in about 60% yield. From either compound, oxime or semicarbazone, only one of the two possible diastereomeric reduction products could be isolated. The inosamine III was readily N-methylated with formaldehyde in formic acid; it gave, with D-glucose, an amorphous, hygroscopic N-glucoside which failed to crystallize, and could not be reduced catalytically at room temperature and atmospheric pressure.

[1] The compounds are being tested for their action against *Mycobacterium tuberculosis* in the Tuberculosis Research Laboratory, U. S. Public Health Service, Cornell University Medical College, New York, N. Y., under the direction of Dr. Bernard D. Davis. An outline of the over-all plan of the cooperative project and methodological aspects will be given elsewhere.

[2] This compound has been prepared recently and independently by Carter, *et al.* (1). For the present we are naming this and analogous compounds inosamines as suggested by the authors.

[3] This compound was found to be identical with a desoxyinositol obtained recently by Magasanik and Chargaff (2) in the catalytic reduction of *rac.-epi*-inosose in acid solution.

Acknowledgment: We wish to thank H. George Latham, Jr., for technical assistance and Herbert E. Carter and Erwin Chargaff for supplying samples for direct comparison. The microanalyses are from the Institute service analytical laboratory under the direction of William C. Alford.

EXPERIMENTAL[4]

rac.-epi-Inosose (I) was prepared by the method of Posternak (3) whose procedure was adapted to 50-g. runs.[5] The optimal time for the nitric acid evaporation was found to be 10–15 minutes (1). The yield of I, purified through the phenylhydrazone, was 10–12%.

Oxime (II) of rac.-epi-inosose (NIH 3582).[6] A mixture of 8.0 g. of hydroxylamine hydrochloride, 11.2 g. of potassium acetate, 6 ml. of water, and 6 ml of absolute alcohol was shaken for ten minutes, cooled in ice, and filtered. The filtrate, diluted to 50 ml. with absolute ethanol, was added during 7–10 minutes to a 75°-solution of 10 g. of I in 75 ml. of water. After 1.5 hours at room temperature, 120 ml. each of absolute ethanol and ether were added. The solution was seeded[7] and left at room temperature for fifteen hours and at −3° for two days. The 7.9 g. of oxime resulting was dissolved in 25 ml. of warm water and 150 ml. of absolute ethanol and 40 ml. of ether were added; yield 7 g., m.p. 150–151° (dec.). For analysis it was recrystallized from 95% ethanol; needles.

Anal. Calc'd for $C_6H_{11}NO_6$: C, 37.3; H, 5.7.

Found: C, 37.5; H, 6.0.

Inosamine (III) hydrochloride (NIH 3489). A mixture of 1.2 g. of II, 0.1 g. of platinum oxide, 10 ml. of water,[8] and 20 ml. of methanol absorbed two moles of hydrogen during twelve hours. To the filtered, methanol-diluted solution was added 0.8 ml. of conc'd HCl and ether to turbidity: yield 0.9 g. (70%), m.p. 220–223° (dec.). It crystallized from water-methanol in prisms of m.p. 223–226° (evac. tube).

Anal. Calc'd for $C_6H_{14}ClNO_5$: C, 33.4; H, 6.6; Cl, 16.5.

Found: C, 33.4; H, 6.5; Cl, 16.5.

When mixed with a sample of *d,l*-inosamine-EA hydrochloride prepared by Carter, *et al.* (1) (m.p. 224–226°, evac. tube), the m.p. was unchanged.

The *free base* (plates, m.p. 204–208.5°, dec.) was prepared from the hydrochloride with aqueous alcoholic ammonia or directly from the filtered reduction mixture by ether-dilution. Attempts to purify it for analysis were attended by gradual decomposition.

The *picrate*, prepared from III with aqueous alcoholic picric acid-ether, crystallized from aqueous alcohol-ether containing a little picric acid, in yellow plates, m.p. 174–176°.

Anal. Calc'd for $C_{12}H_{16}N_4O_{12}$: C, 35.3; H, 4.0.

Found: C, 35.5; H, 3.9.

The *hexaacetate* melted at 188–189° alone or in mixture with that prepared by Carter, *et al.* (1).

The *N-acetyl derivative* had the m.p. 200–201.5° (dec.) (1).

N,N-Dimethylinosamine hydrochloride (NIH 3583). A mixture of 0.2 g. of III, 0.2 g. of 37% formaldehyde, and 0.28 g. of 98% formic acid was heated on the steam-bath for forty minutes, cooled, acidified with six drops of conc'd HCl, and diluted with methanol-ether.

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[4] All melting points, observed in a capillary, are uncorrected.

[5] By H. George Latham, Jr.

[6] Compounds designated by an NIH number have been submitted for testing.

[7] Seed crystals were obtained by further dilution of a small sample with ethanol-ether, washing the precipitated oil with ethanol-ether and finally triturating it with methanol.

[8] With water alone as the solvent, highly colored solutions resulted from which no III could be obtained.

Gradually 0.15 g. (56%) of hydrochloride, m.p. 223–225° (dec.)[9] separated: prisms from aqueous methanol-ether.

Anal. Calc'd for $C_6H_{16}ClNO_5$: C, 39.4; H, 7.4.

Found: C, 39.5; H, 7.3.

The *picrate*, prepared from the hydrochloride with aqueous alcoholic picric acid-ether, was recrystallized from water-ethanol, then 95% ethanol; orange prisms, m.p. 182–184°.

Anal. Calc'd for $C_{14}H_{20}N_4O_{12}$: C, 38.5; H, 4.6.

Found: C, 38.7; H, 4.7.

Other hydrogenations of II. A mixture of 0.5 g. of II, 0.05 g. of platinum oxide, 3.5 ml. of water, and 0.5 ml. of conc'd HCl absorbed 2.6 moles of hydrogen during twenty hours. The filtered solution was evaporated to dryness *in vacuo* to give a partially crystalline residue which, from water-alcohol, gave 0.15% g. (35%) of *desoxyinositol* (IV),[10] m.p. 206–208°; prisms.

Anal. Calc'd for $C_6H_{12}O_5$: C, 43.9; H, 7.4.

Found: C, 43.8; H, 7.5.

A mixture of IV and the desoxyinositol (m.p. 204–206°) prepared by Magasanik and Chargaff (2) and termed by them *d,l-epi-quercitol*, melted at 205–207°.

The filtrate from the 0.15 g. of IV, evaporated to dryness, gave, from water-ethanol, a small yield of *epi*-inositol, m.p. 287–290° (evac. tube), identified by a mixed melting point with authentic material (3).

The *pentaacetate* of IV (acetic anhydride-H_2SO_4, steam-bath heat) crystallized from ethanol in plates, m.p. 123–124.5° or prisms, m.p. 142–143°. The two modifications were interconvertible.

Anal. Calc'd for $C_{16}H_{22}O_{10}$: C, 51.4; H, 5.9.

Found: C, 51.4; H, 5.9.

When II was hydrogenated in 25% aqueous acetic acid, 2.3 moles of hydrogen was absorbed to give *epi*-inositol (25%) and III in low yield.

1-Pentahydroxycyclohexylsemicarbazide (NIH 3518). A mixture of 1.0 g. of I semicarbazone (NIH 3517) (3a), 0.1 g. of platinum oxide, and 50 ml. of water absorbed 1.3 moles of hydrogen during sixty hours. The filtered solution was evaporated to dryness to give a sirup which crystallized from water-ethanol in a yield of 0.6 g.; rectangular plates, m.p. 208° (dec.).

Anal. Calc'd for $C_7H_{15}N_3O_6$: C, 35.4; H, 6.4.

Found: C, 35.4; H, 6.6.

Thiosemicarbazone of rac. epi-inosose (NIH 3788). A mixture of 1.0 g. of I, 0.6 g. of thiosemicarbazide, and 10 ml. of water was heated on the steam-bath for 15–20 minutes, let stand at room temperature for seven hours and at 5° overnight: yield 0.8 g., m.p. 197–198° (dec.): needles from water.

Anal. Calc'd for $C_7H_{13}N_3O_5S \cdot H_2O$: C, 31.2; H, 5.6; H_2O, 6.7.

Found: C, 31.3; H, 5.7; Loss in wt. (117°, high vac.), 6.7.

N-Glucoside of inosamine (NIH 3584). A mixture of 0.5 g. of anhydrous D-glucose, 0.5 g. of III, and 25 ml. of methanol was refluxed for two hours, diluted with ether, and left at 2° overnight to give 0.9 g. of an amorphous, hygroscopic solid. For analysis it was dissolved in boiling methanol (Norit), precipitated with dry ether (prolonged cooling), and dried at 75–80° *in vacuo*: m.p. 110–123° (froth), $[\alpha]_D^{20}$ $-2.5° \rightarrow 16°$ (*c*, 0.40, H_2O, 60 hrs.).

Anal. Calc'd for $C_{12}H_{23}NO_{10}$: C, 42.2; H, 6.8; N, 4.1.

Found: C, 42.4; H, 7.0; N, 4.1.

The change in rotation is apparently due principally to partial hydrolysis (5). When 0.3

[9] In the first experiment a lower-melting modification (m.p. 188–191°) was obtained. It was readily converted to the one of m.p. 223–225°.

[10] An isomeric desoxyinositol melting at 233–235° (pentaacetate, m.p. 190°) was obtained by Posternak (4) in the catalytic reduction (platinum oxide, dil. H_2SO_4) of *scyllo-meso*-inosose.

g. of N-glucoside was allowed to stand for three days in water, 0.05 g. of III was recovered as the hydrochloride. Attempts to hydrogenate the N-glucoside (methanol, platinum oxide, room temperature and pressure) were unsuccessful.

SUMMARY

The catalytic hydrogenation of the oxime of *rac.-epi*-inosose is described. Depending upon the conditions, an inosamine, a desoxyinositol, and *epi*-inositol were obtained in varying amounts.

An N-glucoside has been prepared from the above inosamine.

BETHESDA 14, MARYLAND

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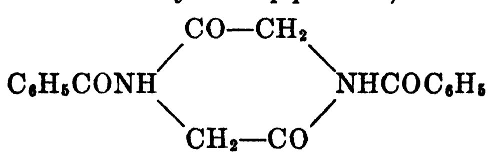
"The Isomerization of Morphine to O-Desmethylthebainone," Ulrich Weiss and Nathan Weiner, *J. Org. Chem.*, **14,** 194 (1949).

After this paper was submitted for publication, we became aware of the preparation, by Pschorr and Hoppe (1), of the "sulfur-free ketone" of the morphine series from β-ethylthiomorphide. Since the corresponding ketone of the codeine series (2) has been identified as thebainone by Morris and Small (3), the ketone from thiomorphide should be identical with our O-desmethylthebainone. The properties reported by Pschorr and Hoppe for their compound are in reasonable agreement with this assumption.

	SULFUR-FREE KETONE (PSCHORR AND HOPPE) M.P., °C.	O-DESMETHYLTHEBAINONE (WEISS AND WEINER) M.P. (CORR.), °C.
Base	215–217 (dec.)	220–221 (dec.)
Oxime	260 (dec.)	274–279 (dec.) (crude product)

(1) *Ann.*, **373,** 45 (1910).
(2) PSCHORR, *Ann.*, **373,** 15 (1910).
(3) *J. Am. Chem. Soc.*, **56,** 2159 (1934).

Constitution of the substance $C_{18}H_{16}N_2O_4$ obtained from hippuryl chloride, pyridine, and copper. In a paper, "The Use of Ketones in the Erlenmeyer Azlactone Synthesis", V. Boekelheide and Lois M. Schramm (1) say that we have assigned formula I to the substance which can be obtained from hippuryl chloride, pyridine, and copper powder, or in other ways (2). In this respect the above mentioned authors are mistaken. Formula I was proposed for this substance by Scheiber and Reckleben (3) and not by us; we only made reference to it (2). Later (4) we expressly emphasized the fact that formula I cannot be correct, as the authentic NN-dibenzoyldiketopiperazine,



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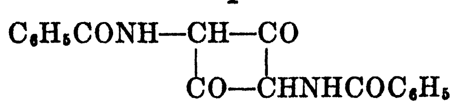
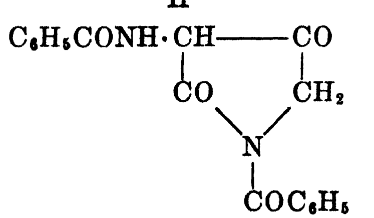


II



III

which has been synthesized by Sasaki and Hashimoto (5), possesses different qualities. Even at an earlier date Rügheimer (6) proposed formula II for the same compound, but this structure also seems not to be correct, as Cornforth and Huang (7) have made formula III very probable.

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(1) *J. Org. Chem.*, **14**, 298 (1949).
(2) *Helv. Chim. Acta*, **11**, 235 (1927).
(3) *Ber.*, **46**, 2418 (1913).
(4) *Helv. Chim. Acta*, **15**, 1420 (1932).
(5) *Ber.*, **54**, 2688 (1921).
(6) *Ber.*, **21**, 3325 (1888).
(7) *J. Chem. Soc.*, 1958 (1948).

ERRATA

"Some Reactions of Amidone," Everette L. May and Erich Mosettig, *J. Org. Chem.*, **13**, 459 (1948). Page 464, line 5, n_D^{20} 1.5888 should read 1.5588.

"1-Dodecanesulfinic Acid," C. S. Marvel and Rayner S. Johnson, *J. Org. Chem.*, **13**, 822 (1948). Page 828, line 11, acetid should read acetic; line 48, the formula $C_{14}H_{28}O_3S$ should read $C_{14}H_{28}O_4S$.

"Studies in the Juglone Series. II. Hydroxy and Hydroxyhalogeno Derivatives," R. H. Thomson, *J. Org. Chem.*, **13**, 870 (1948). Page 876 (near the bottom) (presumably the 2-acetoxy compound) should read (presumably the 3-acetoxy compound).

AUTHOR INDEX

SUBJECT INDEX